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Peptic ulcer

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DEFINITION

Peptic ulcer is an ulcer of the mucous membrane of the stomach or duodenum, or after surgery, of another portion of the gastrointestinal tract, which is bathed by or is in contact with the acid gastric juice.

STATEMENT OF PURPOSE

It is the purpose of this paper to present a fundamental understanding of the condition of peptic ulcer and to lay particular stress upon the more recent trends in the medical treatment for the uncomplicated phase of this condition.

HISTORY

The history of peptic ulcer (13)[1] dates back to the time of Galen, at which time were made observations regarding the existence of round ulcer of the stomach. It was not until the sixteenth century, however, that isolated anatomical descriptions of the lesions appeared. Baillie, in 1793, published the first clear description

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[1]Figures in parenthesis refer to "Literature Cited," page

of the morbid anatomy and symptoms of gastric ulcer. In 1828, Abercrombie of Edinburgh recorded more complete observations of both gastric and duodenal ulcer, with recommendations as to treatment. The classical observations of Cruveilhier presented in his "Anatomie Pathologique du Corps Humain" (1829 - 1835) form the foundations of the present knowledge of peptic ulcer. He was able to make clear the differentiation between cancer and benign ulcer of the stomach. Virchow first employed the term "corrosive ulcer of the stomach" and Quincke introduced the modern terminology of "peptic" or "digestive" ulcer of the stomach. Rokitansky is also another important name in the history of the development of knowledge of the disease. The development of modern aseptic abdominal surgery gave the greatest impetus to progress in the study of peptic ulcer and Moynihan stands foremost among the surgeons and physicians who have contributed so largely to the literature for his original work in the field of gastric and duodenal surgery.

ETIOLOGY

Under etiology (13) are here considered frequency, age incidence, and familial predisposition.

FREQUENCY:- The statement of frequency of peptic ulcer varies somewhat according to the different investigators but

the difference is not great. One important series of autopsies gave the following results. Acute or chronic ulcer or ulcer scars were found in the stomach in 6.9 per cent and in the duodenum in 5.3 per cent of a series of 3,058 cases studied. In another intensively studied series of 1,500 autopsies, 130 cases of gastroduodenal ulceration were found equally distributed between the two organs (4.5 per cent in each). Added to this large percentage of open ulcers were 42 cases having gastric scars and 36 cases showing duodenal scars. As a conservative estimate it may be said that about ten per cent of all individuals at some time during life, have a chronic ulcer of the stomach or duodenum. The surgeons observe duodenal ulcer with considerably greater frequence than gastric ulcer, the ratio being about 1 to 4, while pathologists find a somewhat greater proportion of ulcer scars in the stomach, being about 1.16 gastric to 1 duodenal ulcer. This divergence of figures is undoubtedly due to the fact that duodenal ulcer is more likely to cause symptoms sufficiently distressing to compel the patient to seek medical or surgical relief.

SEX INCIDENCE:- Gastric ulcer occurs with almost equal frequency in men and women, but duodenal ulcer is far more common in men than in women, the proportion being about three to one.

AGE:- The average age of onset of symptoms is about 35 years . It is seldom seen before the third decade, but may occur in any decade.

FAMILIAL PREDISPOSITION:- Careful inquiry into the family history of ulcer cases discloses either positive or presumptive evidence of ulcer in two or more members of the family in a remarkable number of instances.

PATHOGENESIS

There are many factors (64) regarding the etiology, course, and chronicity of the lesions of peptic ulcer which are imperfectly understood. A brief review of the literature on the subject is convincing evidence of the complexity of the problem. It is my purpose here to review a few of the more important hypotheses advanced to explain the development and course of peptic ulcer.

CIRCULATORY DISTURBANCES:- It was Virchow who fathered the impression that disturbance of the veins and arterioles of the submucosa resulted in localized necrosis of the muscularis and the mucous membrane. The peptic action of the acid gastric chyme would then cause the ulceration. More recently it has been suggested that hemorrhagic infarcts are the immediate pathologic processes that eventually result in necrosis of the gastro-intestinal mucosa. An anemic spot on the anterior surface of the duodenum has been described and it is believed that this area might be increasingly vulner-

able to the development of ulceration because of circulatory deficiency. Poor vascularization of the pyloric portion of the lesser curvature of the stomach has also been noted and is suggested that in consequence of this there may be localized ischemia with increasing vulnerability of the tissues to vascular insults. Chronicity might well be related to the impoverished vascularization of the pylorus and the first part of the duodenum. Attenuation of the speed of the blood current as it traverses the small arteries of the mucosa has been noted which might render the areas particularly liable to local embolism and thrombosis. It has been found that tying off large vessels to the stomach occasionally results in acute ulceration in the areas supplied by the vessels. Investigators have found that the introduction of a dilute solution of formaldehyde into the small gastric artery often results in chronic and even perforating gastric ulcers. This procedure greatly narrowed the lumen of the affected vessels, the blood supply to localized areas within the wall of the stomach thus being decreased. Clamping the mucosa of the duodenum for thirty minutes produces acute ulcers there.

EROSION OF TISSUE BY ACID:- Many investigators have pointed out the part played by the eroding action of abnormally acid gastric juice in the production and persistence of peptic ulceration. Lesions have been found confined almost

entirely to the protions of the stomach and duodenum that are habitually bathed with acid chyme. The assumption has been made that hyperacidity of the gastric secretion injures the wall of the stomach in the region of the fundic glands, particularly in the region of the lesser curvature, and that the wall of the intestine is likewise susceptible to similar trauma, whereas within the stomach the portion including the pyloric glands seems to be partly protected. It has also been assumed that psychically stimulated gastric juice is the cause of erosions of the mucosa.

In most instances, experiments in the production of peptic ulcer have resulted in the production of acute ulcers or mucosal erosions which had a tendency to heal rapidly and which, as a rule, did not have the general characteristics of ulcers in man. Mann and Williamson described a method for producing in animals a chronic ulcer which was similar in most respects histologically to peptic ulcer in man. They drained duodenal secretions, as well as the bile and pancreatic juice, into the terminal part of the ileum and then transplanted loops of jejunum or ileum into the position usually occupied by the duodenum. Following this procedure, subacute ulcer usually developed beyond the pylorus in the jejunal mucosa just distal to the line of suture. Mann and Williamson believed that the chemical action of the acid

chyme, which was undiluted by duodenal content, on the jejunal muccus membrane was the cause of the ulceration, and that the mechanical factor or impingement of the acid chyme on the jejunum, through the pylorus, had an effect in producing the lesions and in particular, perhaps, in determining the site of the ulcers.

The following experimental work gives added corroboration to the factor of acid erosion as a cause in the production of ulcer. A counterpart of the ulcer of Meckel's diverticulum in man was produced by implanting a small isolated pouch of gastric wall into the jejunum and ileum. This resulted in progressive ulcers in the jejunum in 85 per cent of the experiments, and when the isolated pouch was implanted into the ileum, in 100 per cent. The result was cited as a remarkable example of the susceptibility of an organisms living tissue to the irritating action of pure, undiluted gastric juice. A similar gradient in susceptibility was suggested by attaching a piece of ileum to an isolated gastric pouch and producing ulcer in practically all experiments. The same operation was performed by using strips of duodenum, and found that the upper part of the small bowel was much more resistant to the acid-eroding action of the gastric pouches, and that ulcers occured much less frequently. Experimental work thus gives conclusive evidence that the eroding action of undiluted gastric juice

is undoubtedly one of the chief factors in the production of chronic ulcer.

INFLAMATION AND INFECTION:- Many other investigators have stated their belief that duodenal and gastric ulcers are the results of inflammatory processes, with destruction of tissues, which begin at the surface of the mucous membrane and from there gradually spread into the depths of the tissues. They are of the opinion that lesions never develop in healthy mucosa, but always as a result of gastritis or duodenitis. Pus injected intravenously into experimental animals produces acute lesions in the stomach and duodenum. Pure cultures of streptococci and staphylococci produce the same effect. Feeding colon bacilli to dogs over a long period of time produces round ulcers of the stomach and duodenum. In 1913, by intravenous injection of streptococci of the proper grade of virulence, Rosenow produced ulcer of the stomach and the duodenum in animals; he believed that the ulcers were due to a localized infection and a secondary digestion of the gastric mucosa. He later advanced the hypothesis that the usual form of gastroduodenal ulcer may be due to a localized infection by streptococci having a special elective affinity for the mucous membrane of the stomach and the duodenum. In 1924, he reported the isolation, from excised ulcers and from foci of infection in pa-

tients suffering from peptic ulcer, of streptococci which had a selective affinity for the stomach and duodenum when they were injected into animals and which in many instances produced hemorrhage and ulceration. Further evidence corroborating that of Rosenow was that of producing chronic foci of infection in dogs by devitalizing some of their teeth and making injections into them of streptcccccci obtained from the infected teeth of patients suffering from ulcer of the stomach. Hemorrhage or ulceration of the gastroduodenal mucosa was produced in many of these dogs.

NEUROGENIC FACTOR:- Many observers have considered that derangement of the nervous system was the most significant single factor in the causation of peptic ulceration. Some derangement of the function of the sympathetic and parasympathetic nervous system is considered by advocates of this hypothesis to result eventually in localized spasmophilia of the duodenal or gastric musculature, with consequent areas of mucosal or submucosal ischemia. In consequence, there is a diminished resistance in the localized areas which results eventually in erosion of the mucosa. The prolonged continuation of this nervous irritability tends to the production of chronic ulcer. Some think there may be an actual neuritis of the vagus nerve contributing to ulcer formation. Section of the vagus nerve definitely decreases,

at least for a time, the acidity of gastric secretion.

It might thus be postulated that the increase in the activity of the vagus nerve brought about by increasing the rate of secretion of the gastric acids tends to increase the incidence of ulcer. Dissection of the vagus nerves of the stomach prevents the occurrence of ulcers in some instances following certain operations which would otherwise tend to produce ulcers. Irritative disturbance of either fiber tracts or vagal centers in the brain stem may be responsible for ulcer in certain instances.

ULCER DIATHESIS:- Many investigators have observed that certain persons are particularly liable to the development of peptic ulcer; this has led to the postulation that there must be some definite anatomic or physiologic abnormality which increases the susceptibility of these persons to the development of ulcer. Draper stated that certain anthropometric relations as well as certain psychologic factors are characteristic of the ulcer-bearing patient, and he referred to the belief that there is something characteristic in the appearance of the patients. Their faces are usually thin and drawn, with high malar prominences; they are poorly nourished and energetic in demeanor, and present an anxious expression. Other observers believe that a "vasoneurotic diathesis" is the required condition preceding the development of peptic ulcer.

Müller and Heimberger examined fresh specimens with a capillary microscope immediately following partial gastrectomy. They found spasm and atony of the arterioles, capillaries and venules of the gastric mucous membrane. They intimated that they could also demonstrate similar vascular abnormalities in the mucous membrane of the lips and in the skin of their patient. They assumed that this diathesis was the result of congenital or acquired disharmony in the structure and the function of the peripheral blood vessels.

Hurst and Stewart described hypersthenic gastric diathesis and intimated that it is an inborn variation from the average normal which manifests itself in a short stomach accompanied by active peristalsis and rapid evacuation, and in hyperchlorhydria with gastric hypersecretion. Although they admitted that the condition is compatible with the perfect function of the digestive organs, they expressed the belief that it is one of the essential predisposing factors in the production of duodenal ulcer. They stated that persons with long stomachs, if exposed to the exciting causes of ulceration, are likely to have gastric rather than duodenal ulcers.

VARIOUS HYPOTHESES IN THE PROBLEM OF ULCER IN MAN

In reviewing the various hypotheses advanced by physiologists to explain the genesis of ulcer, it must be mentioned

that the hypotheses usually represent successful efforts in the production of ulcer in experimental animals. No doubt much valuable information is thus acquired, but it is difficult to condense and correlate it into the problem of ulcer in man. Confusion soon results when an attempt is made to apply a specific single cause for ulcer to the heterogenous clinical complexities of the behavior of the syndrome initiated by ulcer in man.

In all probability, the picture puzzle of ulcer will be satisfactorily conjoined only by the application and the correlation of the combined knowledge accumulated by physiologists, pathologists, surgeons and clinicians. When the information obtained by physiologists withstands the critical analysis of clinicians and is practical in its application to the diverse problems of ulcer in man, and when clinical facts can be taken by the physiologist and correlated with experience in the laboratory, the disjointed segments of the puzzle of peptic ulcer will have been approximated to the ultimate solution of this most important problem.

A careful analysis of the causes assigned for the formation of ulcer reveals that many are not at all applicable to the problem of ulcer in man, and that others apply only in a limited degree. An attempt is made to rearrange certain of the important hypotheses concerning the formation of

ulcer into a clinical classification which seems applicable to the problem in man. Peptic ulcer is probably the result not of a single factor but of several interacting factors; these will be considered separately. The factors can best be summarized under three heads: the factor of trauma to tissue, the factor of aggression and defense, and systemic factors.

FACTOR OF TRAUMA TO TISSUE:- Under this heading can be considered all the traumatizing influences which cause or accompany the original aberration from its normal state in the mucous membrane or in the wall of the viscus. There may be involvement from the mucosa downward. There may be disturbances in the submucosal tissue, which by virtue of its consequent loss of resisting potentiality will the more readily disintegrate and succumb to the eroding process. Various experimenters have amply demonstrated that there are numerous ways in which this can be brought about. One illustration presents itself in the work of Rosenow, who postulated septic emboli settling as tiny nests in the depths of the tissue, progressing there into bundles of inflammatory islands, destroying the resistance of the local tissue and thus leading to ulceration. Other locally active factors can readily be supplied by vascular spasm, local spasmophilia of the muscles, irritating substances which are in-

gested and cause mucosal injury, and various other mechanical and chemical precesses through which injury to the tissue may occur. Frequently gastric ulcers arise in association with foreign bodies, such as bezoars. Furthermore, ulcers are rather common complications arising in conjunction with diaphragmatic hernia at the point of maximal mucosal irritation. They present good examples of the ulcers arising mainly from local trauma to tissues. Single insults to tissue from whatever cause can produce disturbances which may cause symptoms and serious complications. No doubt hemorrhage or even perforation can be the result of single attacks on gastro-intestinal tissue. Chronic ulcer, however, is rarely the result solely of such trauma. The acute lesions heal rapidly unless some perpetuating factor of persisting injury to tissue comes into play.

Areal inflammatory lesions, mucosal erosions and acute ulcers probably can result from local insult to tissue, but they most likely represent only one of the causes, or one of the stages, of chronic ulcer. For the completed accomplishment of chronic ulcer they need assistance from other factors which keep the original lesions from healing.

FACTORS OF AGGRESSION AND DEFENSE:- The only common denominator which is consistently and readily applicable to the lesions is that they occur in tissues bathed by the acid

gastric chyme. When tissues other than those naturally accustomed to the chemical and mechanical action of gastric juice are exposed to the aggression of the acid chyme, the potentiality for ulceration promptly develops. Obviously, certain factors must arise which change either the resistance of the tissues to the eroding action of the peptic juice or the nature of the chyme so as to heighten its eroding potentialities. It is also evident that the change of balance is not permanent or invariably active in the same degree, because alternation of healing and activity is one of the inherent characteristics of the lesions. In many instances the ulcerating process terminates spontaneously, leaving only a scar to bear witness to the fact that anything unusual has occurred in the area. During the usual normal physiologic cycle the factors of aggression included in the eroding potentialities of the acid gastric chyme are amply counteracted by gastroduodenal tissues which satisfactorily protect themselves against this digestive action. So long as the balance between the defense of tissue and the aggression of acid chyme is properly maintained, nothing unusual happens. If one tips the scales, however, by heightening for a considerable period the factor of aggression or destroys in some way the mechanism of defense, it is conceivable that erosion of tissue will take place. Physiologists have amply demonstrated the increased vulnerability

of tissues to the eroding action of the gastric chyme which has greatly accentuated acid-pepsin values. The more successful they are in obtaining acid chyme free from intragastric or extragastric diluents, the surer they are of producing erosions and ulcers in tissue exposed to these juices. They have furthermore demonstrated that tissues unaccustomed in their normal physiologic existence to the eroding actions of the acid chyme will succumb more surely and quickly.

The resistance of the jejunum, ileum and colon to the chemical action of undiluted gastric juice decreases progressively from the jejunum to the colon. It is of significance that factors of aggression which in themselves are inadequate to produce ulcers when tissues are naturally protected are capable of producing ulcers in tissues not so protected.

If trauma were caused by infected emboli, vascular spasm or mechanical irritation of the tissue which, normally is amply resistant to the acid factor of aggression, or if these eroding potentialities were intensified for a considerable period by oversecretion or underdilution, the physiologic requirement for the development of ulcer would seem to be completed. Certainly these factors would produce ulcer in animals, and there is no reason to assume that any other result would occur in man. These factors of aggres-

sion and resistance are applicable in the case of esophageal ulcer; with increased vulnerability of tissue and the infection and regurgitation of acid chyme, erosion may easily occur there. Similarly, the peptic ulcers occurring about heterotopic gastric tissues, such as are occasionally demonstrable in the vicinity of Meckel's diverticulum, are practically always found in contiguous regions that are called on to resist the full aggression and irritation of the secretory products of these tissues. Since the tissues are not intended by nature to counteract the aggression of these secretory irritants, they seem to succumb more easily to chemical insults of this type.

SYSTEMIC FACTOR:- It is possible to produce in experimental animals physiochemical abnormalities which can readily be applied to the problem of peptic ulcer in man. Substantial corroborative evidence of the importance of the two factors just considered are available from experimental laboratories. There are, however, certain biologic phenomena to which man alone is heir. It has been observed that during periods in which the general health of patients has been undermined, the liability to development or recurrence of peptic ulcer seems to be appreciably accentuated. Frequently, with improvement in general health, there is less difficulty in controlling the symptoms, and the ulcer pro-

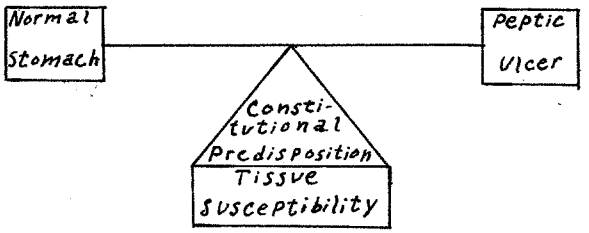
gresses rapidly to a quiescent state. In reviewing the histories of patients with peptic ulcer, it is not uncommon to find that the origin of symptoms occurred during periods of diminished resistance, and frequently the patients have noted that periods of reactivation correspond exactly to periods during which they were in the throes of some acute infection. The application of a yardstick to measure physical characteristics in the patients prone to the development of ulcer has not been very successful, because the factor of greatest importance seems to be one which is more psychophysiologic than physical and which can be measured anatomically and physically only with great difficulty. Moreover, this factor seems to be fluctuating rather than constant. The syndrome of ulcer is characterized by periodicity and intermittency, and many chronic ulcers advance to complete cicatrization and healing; therefore, the factors which are at one time capable of producing and activating the lesions finally may cease to exert their influence and allow the ulcer to go on to quiescence or even to complete and permanent healing.

The characteristics so often duplicated in cases of peptic ulcer seem especially noticeable in cases of duodenal or anastomotic ulcer. There is a striking uniformity of temperament, but even more striking is the similarity of mental reactions. Whether to consider these responses phy-

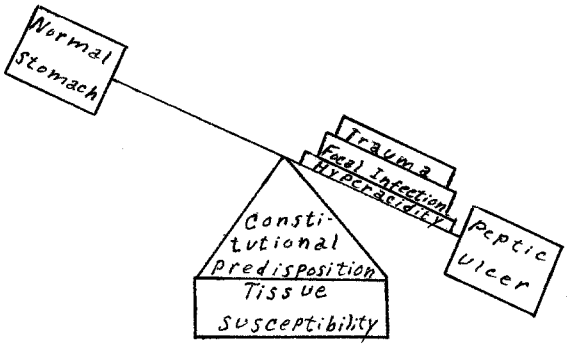
siologic or psychologic seems of no great ultimate importance, since the two types are inseparable and in the end are probably cause and effect in reversible possibilities. The behavior and reactions of the patients are similar, and they conduct their affairs with like dispatch. They are unusually alert, attentive and keen, and frequently appear a bit stimulated, often resembling patients with moderate hyperthyroidism. They are ambitious, intensive, driving and high-strung. They are persistent in their activities, relentless in the pursuit of their objectives and forgetful of their physical requirements when they are busy with their occupational routine. They are likely to carry on despite obstacles until nervously and physically exhausted. Because of their persistence and ambition, they are frequently successful in their activities. They are, as a rule, willing to accept unusual responsibilities and often live persistently in an environment conducive to the development of great mental tension.

Curiously enough, the desirable virtues of the modern, intensive, aggressive American, the characteristics which have been eulogized and designated as the cardinal marks of American successes, are precisely the characteristics so often reduplicated in the ulcerous type of patient. Because a premium is paid for these characteristics, an ever-increasing number of persons will acquire them and so develop this disease.

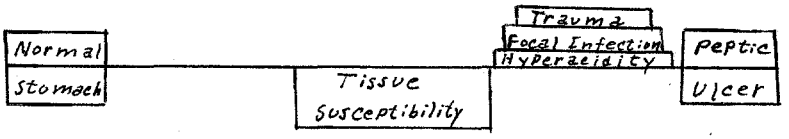
The following are interesting diagrammatic representations (59) pertaining to the development of peptic ulcers.



1. Diagrammatic drawing showing normal balance in a patient with tissue susceptibility and constitutional predisposition. Unless there are additional precipitating factors, constitutional predisposition and tissue susceptibility will not produce peptic ulceration.



2. Diagrammatic drawing illustrating production of peptic ulcer in a patient with the predisposing factors, tissue susceptibility and constitutional predisposition and, in addition, the precipitating factors, hyperacidity, focal infection, and trauma. Following the removal of the precipitating factors, the normal balance is again resumed, as shown in figure 1, even though tissue susceptibility and constitutional predisposition persist.



3. Diagrammatic drawing showing the normal balance maintained even though the precipitating factors, hyperacidity, trauma, or focal infection, are present in an individual without constitutional predisposition. Even though the precipitating factors are present, the patient does not develop an ulcer.

PATHOLOGICAL ANATOMY

The two great divisions of peptic ulcer are gastric and duodenal and their pathological characteristics (13) vary with their duration and stage of development.

The great majority of gastric ulcers are situated along the lesser curvature or in close proximity to it, the posterior wall ranking next in frequency of involvment. Chronic ulcer of the fundus and greater curvature are rare.

Duodenal ulcers are confined to the first portion, the so-called duodenal bulb. They are rarely found more than two inches from the pylorus and tend to involve with practically equal frequency the posterior and anterior walls.

Ulcers of the stomach and duodenum are usually single. However, post-mortem records show that in approximately 25 per cent of cases two or more ulcers are present and even

three or more are not uncommon.

More than 90 per cent of simple chronic gastric ulcers measure less than 2.5 centimeters in diameter and they are not seen over 4 centimeters in diameter. Duodenal ulcers are relatively smaller, the larger ulcers being found in the posterior wall.

In its early stages peptic ulcer has a characteristic appearance, tending to a round or oval form, with a sharply defined, flat margin almost devoid of inflammatory reaction and with a base varying in appearance according to the depth and stage of development of the ulcer. When healing fails to occur, there is a marked tendency to progressive digestion by the gastric juice of the deeper layers of the wall and of the margins of the ulcer, an inflammatory reaction in the surrounding tissue is established, and gradually the stage of typical chronic peptic ulcer is reached, associated with more or less inflammatory edema and engorgement of the blood vessels.

SYMPTOMS

The chief clinical symptoms of ulcer (14) are pain, vomiting, and hematemesis, and of these the really important one is pain.

PAIN:- The extremely significant feature with regard

to the pain is its punctuality. In the same patient, after the same meals it appears with the most exact regularity, after the same intervals of comfort. In cases of gastric ulcer the pain, which after an interval follows the taking of a meal, usually disappears gradually before the next meal. In cases of duodenal ulcer the pain is apt to come on after an interval following a meal and continue until food is again taken. During the pain, food and soda characteristically give relief in both types of ulcer.

The pain is usually located behind the xiphoid process or in the epigastrium. In character it is sometimes agonizing, but more often dull and merely a sensation of burning or discomfort. In a considerable number of cases pain is absent.

VOMITING:- This symptom usually occurs when the pain is most severe. It is seen in less than 50 per cent of patients with ulcer, and is usually not associated with the uncomplicated duodenal type.

BLEEDING:- While bleeding is very common, hematemesis occurs in hardly more than 10 per cent of all cases. Melena indicates extensive bleeding in about 25 per cent of patients.

APPETITE:- The appetite is usually normal but may be increased. Nutrition remains unchanged in the uncomplicated case. In duodenal ulcer true bulimia is sometimes seen. The

usual dyspeptic symptoms, pyrosis, belching, and fulness and discomfort after meals, may or may not be present and are not characteristic.

OBJECTIVE FINDINGS:- Of the objective findings, the most important are tenderness on pressure of the epigastrium, changes in the gastric contents, the conditions revealed by x-ray, and the character of the stools. The presence of occult blood in the stool when the diet is free from meat and there is no bleeding in the rectum, mouth, or pharynx, is extremely significant.

DIAGNOSIS, COMPLICATIONS and SEQUELAE

In a large proportion of cases duodenal ulcer, and, in a smaller proportion, gastric ulcer can be diagnosed (13-14) with almost absolute certainty. The periodicity of the attacks, especially when ulcer is duodenal, the punctuality of the pain, the exacerbation of symptoms by ingestion of course and highly seasoned food, their relief following the taking of alkalies and bland food, and their mitigation and often temporary disappearance following restriction to a soft, bland diet, the presence of occult blood in the feces, pain on pressure over the duodenum or stomach, hyperacidity and hypersecretion, and the characteristic changes in the x-ray shadow all make great certainty of diagnosis possible. A

small percentage of duodenal ulcers, and a larger percentage of the gastric type, produce symptoms which are very confusing, atypical, and not in the least suggestive of ulceration.

For purposes of diagnosis it is well to distinguish between simple, uncomplicated gastric and duodenal ulcer and ulcer in which the sequence of pathological changes has been such as to cause various associated structural changes capable of more or less profoundly modifying the usual symptom picture of uncomplicated ulcer. Careful investigation should be made in each case for evidence of the following complications and sequelae of ulcer: (a) pyloric obstruction, resulting from cicatricial narrowing, inflammatory swelling and edema of the tissues about the ulcer or from spasm of the pyloric sphincter; frequently all three of these obstructive factors are present in varying degrees, and it is necessary to differentiate clearly between the causes of obstruction, namely spasm and swelling, and the fixed stenosis of an unyielding cicatrix; (b) excessive continued secretion of gastric juice; (c) perigastritis and periduodenitis; (d) perigastric and periduodenal adhesions; (e) perigastric and periduodenal abscess; (f) hour-glass deformity of the stomach; (g) perforation; (h) hemorrhage; (i) secondary carcinoma.

In differential diagnosis diseases of the gall-bladder and urinary apparatus, nervous indigestion, various intestinal lesions, such as appendicitis, adhesions and intestinal

parasites, carcinoma, pancreatitis, gastroptosis, epigastric hernia, and perhaps even conditions associated with marked chronic constipation, may cause confusion.

PROGNOSIS

The prognosis (45) for life in this disease is good. It is rarely fatal, having a mortality of only 3 to 6 per cent and these deaths usually resulting from one of the many possible complications.

Peptic ulcer is a constitutional disease with a local manifestation of ulceration in the gastro-intestinal tract. Disappearance of the ulcerations tend to occur periodically with or without treatment and should be considered only as a remission and not as a cure. A peptic ulcer patient can never be assured against a return of the ulcer and symptoms because he retains a predisposition which always remains as a part of his constitution to menance him. The chance of a given remission occurring is excellent, with or without treatment, in uncomplicated cases, and especially in the more recent cases. The average peptic ulcer case reaches or surpasses the mean life expectancy.

The prognosis as concerns morbidity is extremely bad. The gravity of the condition lies in the suffering, the restriction of activity and diet, and the economic threat.

The prognosis further depends on the location of the patient, being better in this country in the South and West, and on the economic status which can provide rest and composure, vacation and travel, proper nursing and diet.

T R E A T M E N T

Every ulcer of the stomach or duodenum with which the physician and surgeon is called upon to deal, barring the more acute perforating and hemorrhagic types, is an ulcer which in the early months of its development would have healed readily under simple medical measures. The early diagnosis and appropriate treatment of peptic ulcer should be a primary objective in the effort to lower the mortality and lessen the suffering and great economic loss resulting from the progressive pathological changes which occur in the chronic stages of gastric and duodenal ulcer.

The decision of how an ulcer should be treated (8,13,17), whether by medical measures or by referring to the surgeon for operation, should be based upon a careful study of the conditions existent in the individual ulcer patient.

SURGICAL TREATMENT

According to most authors there appear to be certain definite specific indications for surgery. These consist primarily of complications of ulcer. They are: (a) perforation into the peritoneal cavity, (b) perigastric abscess, (c)

reasonable suspicion of the development of carcinoma at the site of gastric ulcer, (d) cicatricial pyloric obstruction to such extreme degree as to preclude the possibility of maintenance of a fair state of nutrition, (e) large, deeply penetrating gastric ulcers which fail to heal completely under medical treatment, and (f) chronic pancreatitis.

Relative surgical indications appear to be: (a) cicatricial pyloric obstruction of such a degree that the evacuation time of the stomach is delayed appreciably, (b) recurrent massive hemorrhages, (c) recurrent gastric ulcer, (d) gastric and duodenal ulcer of considerable chronicity in patients who for any reason are unable to carry out the essential details of medical treatment for a period of months, (e) chronic nephritis with serious impairment of renal function, and (f) hour-glass stomach.

The earlier treatment is given, the better is the chance of a satisfactory result. It is the contention, therefore, of Farquharson (28), that surgery should not be put off indefinitely if medical treatment proves unsatisfactory, for surgery done late in the process is more apt to give an unsatisfactory result than if done early. It is his belief that if a satisfactory remission does not ensue after one thorough therapeutic test in cases of duodenal ulcer, surgery should be done unless there are definite contraindications.

Perhaps a good rule to follow would be (35) to not carry patients in a state of semi-invalidism to long on medical therapy, and to not operate as long as the patient can be maintained in good health on non-surgical therapy. There are those (76) who believe that no uncomplicated peptic ulcer should recieve surgery.

According to Tidy (76), surgery can offer a higher proportion of definite, and what may be called permanent, cures than can medicine, but the percentage is not high. The immediate operative mortality is about 5 per cent, with an additional late mortality which is not less. The risk of the serious sequela of gastro-jejunal ulcer is uncertain, but on the results of the short follow-up of St. Bartholomew's Hospital, and the longer results of the Peter Bent Brigham Hospital, it can scarcely be less than 10 per cent and may be appreciably more. Compared with these serious surgical risks there is under medical treatment a risk of fatal perforation which does not exceed 4 per cent over prolonged periods. The expectation of working capacity is somewhat greater on surgical than on medical treatment. Thus surgical treatment can offer more chance of a "satisfactory" result and a relative immunity from perforation, but unless these statistics posses some extensive flaw, it is a serious responsibility to advise operation for duodenal ulcer in

view of the operative mortality and the risk of gastro-jejunal ulceration.

Gastric ulcer is a more serious condition than duodenal ulcer. There is no appreciable difference between medical and surgical treatment in the chance of a satisfactory result or the expectation of working capacity subsequent to the period of treatment, but the operative mortality under favorable circumstances may approach 20 per cent. Unless again, there is a serious flaw in these statistics, it is a grave responsibility to advise a patient with gastric ulcer to undergo an operation which involves a very high mortality and has no subsequent advantage over medical treatment.

According to this author, evidence is lacking to support the view that cases which are medical failures will in general do better permanently after operation, or will do sufficiently better to counterbalance the operative mortality and risk of gastro-jejunal ulcer.

MEDICAL TREATMENT

The treatment of peptic ulceration has been unsatisfactory because, in too many instances, attention has been focused on the ulcer itself without the realization that the ulcer is only a part of a more generalized condition. Unless the patient as a whole is treated, the results from

therapy are likely to be unsatisfactory. The immediate causes for peptic ulcer (59) can be divided into two groups: one in which the factors are not amenable to therapy but which are inherent and predisposing, and the others which are precipitating but which are controllable. The inherent or predisposing factors are: (a) tissue susceptibility and (b) constitutional predisposition. The precipitating factors are: (a) hypersecretion, (b) hyperacidity, (c) focal infection, and (d) gastric trauma.

Tissue susceptibility, which is an inherent quality present in all individuals, is the vulnerability of certain portions of the gastro-intestinal tract to peptic digestion, such as the lesser curvature, pylorus, duodenal cap, jejunum, and other portions of the intestinal tract subjected to the acid gastric chyme, as Meckel's diverticulum containing islands of gastric mucosa. Constitutional predisposition, although difficult to define is unquestionably present in most if not all patients with chronic gastroduodenal ulceration.

As the predisposing factors are not controllable, or not amenable to therapy, the treatment of a patient with peptic ulcer consists of the prevention and the correction of the precipitating factors, hypersecretion, hyperacidity, focal infection, and gastric trauma. The peptic ulcer

patient must abstain from those activities which increase gastric secretion and acidity; such as smoking, especially cigarettes, ingestion of alcohol and condiments. In addition to the abstinence from those activities which provoke hypersecretion and hyperacidity, neutralization of gastric acidity is to be favored. As we shall see there are many ways in which this may be done, some having greater merit than others. All foci of infection should be removed, because they can act either directly by producing a specific inflamation in the stomach or duodenum, or reflexly when within the abdomen by producing pylorospasm. In order to minimize gastric trauma, only bland foods containing no roughage should be allowed.

Because of the constitutional predisposition to ulceration, it is imperative that the patient change his mode of living for the rest of his life, for recurrences can be expected unless the precipitating factors such as hypersecretion, hyperacidity, focal infection, and gastric trauma, are prevented throughout the life of the patient.

TREATMENT BY DIET AND NEUTRALIZATION

Cruveilhier (1791 - 1874), distinguished pioneer (13) in the field of gastric pathology, advocated an exclusive milk diet in the treatment of peptic ulcer, and milk has

continued to form the basis of the dietary management to the present day. It contains all the elements essential to a suitable diet. Moreover, its peculiar adaptability to the treatment of ulcer lies in the fact that it contains sufficient protein to enable a given volume of milk to neutralize approximately an equal volume of 0.3 per cent hydrochloric acid, so that milk may be used not only as the principle item of nutrition but as the chief acid-neutralizing agent as well.

Later von Leube (1843 - 1912), the noted German physician (17 & 49), devised a regimen for the treatment of peptic ulcer which was used quite extensively for a time. This regimen included not only a carefully planned dietary regulation, but also rest in bed, a morning drink of Carlsbad water (a natural saline spring water), and hot applications to the abdomen. His "cure" was divided into four periods, during the first part of which the patient was fed every two hours. The diet of the first period was limited to boiled milk, bouillon, strained barley water, predigested foods, beef extract and zweiback or crackers. The second diet, which was begun after about ten days included all of the soft foods listed above, to which were added gruels, rice, farina, soft eggs, calves' brains, squab, and tender chicken. At the end of another week, on the seventeenth or

eighteenth day, the third diet was started; this merely contained in addition finely sliced raw ham, beef steak, potatoes, and tea or coffee. The fourth diet, which was begun about the twenty-fourth day, permitted feeding at somewhat longer intervals, and included in addition to the food enumerated above, broiled chicken or squab, roast beef, venison, macaroni, and ordinary white breads. During this last period the patient received about five meals daily. Following this vegetables were permitted. Dietary supervision was maintained for a period of six months.

Lenhartz (1854 - 1910) thought that the Leube treatment was too weakening since there are only 350 to 1200 calories a day provided in the first fourteen days of that treatment. He advocated a treatment (17 & 49) bearing his name, which calculated to supply an adequate caloric intake from the beginning. His assumption was that treatment should begin on the day a hemorrhage occurred. The treatments of thirty years ago were all constructed in fear of starting new hemorrhages by the introduction of food into the stomach. Lenhartz was a pioneer in showing that food could be given immediately. In this diet milk and eggs are the first foods permitted, and then other articles are gradually added. The milk is advocated at first in teaspoonful doses. The eggs are beaten up entire with some sugar, and the cup containing them is put on ice. Lenhartz believed in the bind-

ing power of egg albumin and other proteins for hydrochloric acid, so his diet contains a great deal of protein. He advocated 30 grains of bismuth subnitrate three times a day, for the first ten days, to coat the ulcer. In his endeavor to prevent all intestinal activity he encouraged constipation, even to the extent of permitting the patient to go several days without a bowel movement. Following is a chart outlining the Lenhartz diet.

In 1915, Dr. B. W. Sippy (1866 - 1924) of Chicago (49&74), gave out a technic for the medical treatment of ulcer which he had used for twelve tears, and which gave him justification for believing that most ulcers, even those usually regarded as surgical, could be successfully relieved and healed by this method. The technic has been very widely adopted by American clinicians, and has been enthusiastically endorsed by some of the most conservative of them. It is based in general upon the principle of the practically complete neutralization of the acidity of the gastric juice and is the first scientific attempt to control continuously the reaction of the gastric content. He believed thoroughly in excess acidity causing the ulcer, or at least causing its continuance.

It was his belief that the serious defect in the Leube, Lenhartz, and all other types of medical management, in

The Lenhartz Diet

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Eggs	2	3	4	5	6	7	8	8	8	8	8	8	8	8
Sugar with egg			20	20	30	30	40	40	50	50	50	50	50	50
Milk c.c.	200	300	400	500	600	700	800	900	1000	1000	1000	1000	1000	1000
Scraped beef, gm.						2X35	2X35	2X35	2X35	2X35	2X35	2X35	2X35	2X35
Milk and rice						100	100	200	200	300	300	300	300	400
Zweiback								20	40	40	60	60	80	100
Raw ham										50	50	50	50	50
Butter										20	40	40	40	40
Calories	280	420	637	777	955	1135	1588	1721	2138	2478	2941	2941	3007	3073

general use the world over at that time, lay in the lack of accurate knowledge of what was actually being accomplished while the patient was under treatment. As a rule, if the pain and other symptoms were well controlled, no attempt was made to determine accurately how much, if any, the duration or intensity of gastric juice corrosion was reduced. Pain of ulcer may be entirely absent when the aspirated stomach contents show varying, even high grades of free hydrochloric acidity. The peptic corrosion, according to Sippy, that occurs when a small quantity of free hydrochloric acid is present is approximately as great as when a high degree of free acidity exists.

The digestive action of the gastric juice is due to the solvent action of pepsin on albuminous substances that have been properly permeated by hydrochloric acid. Pepsin is practically inert in alkaline and neutral mediums. It acts slightly in the presence of a combined acid medium, but combined acids are incapable of preparing albumins properly for the action of pepsin. A free acid, such as hydrochloric acid, is required to permeate the albumin and prepare it for the full action of the peptic ferment. Pepsin exerts no appreciable solvent or digestive action on the raw and exposed surfaces of a gastric or duodenal ulcer in the absence of free hydrochloric acid.

The principle involved in the treatment advocated consists essentially in efficiently shielding the ulcer from the corrosive effect of the gastric juice. This is accomplished by maintaining an accurate neutralization of all free hydrochloric acid, thus rendering the digestive action of the gastric juice inert from 7 A. M. until about 10:30 P.M., or during the entire time that food and the accompanying secretions are present in the stomach. In addition, it is accurately determined whether an excessive night secretion is present. If so, this is removed each night until the irritability of the gastric glands has subsided. This applies almost entirely to cases of duodenal and pyloric ulcer that have been associated with stagnation of food and secretion for one or two months, and longer. Such cases almost invariably are attended by a more or less copious continued secretion during the night, which should be removed by aspiration two or three times each night, if necessary. Usually after three or four days of accurate control of free acidity the excessive night secretion disappears. Subsequently the normal quantity (about 10 c.c.) of gastric juice present in the stomach during the night is left undisturbed. The neutralization of hydrochloric acid is accomplished by frequent feedings and the use of alkalies in carefully regulated but adequate quantities. Experience in applying the method to all types of individuals under widely varying con-

ditions has abundantly demonstrated that the corrosive or digestive action of the gastric juice can be thus annulled until healing of the ulcer is accomplished in most cases.

Following is given the Sippy regimen for non-obstructive ulcer treatment.

1. Rest in bed for three weeks. The patient may sit up part of the day, and after the first week take short walks.

2. Diet: a mixture of equal parts milk and cream is the only food at first and is kept cold. It will be called here the M-C mixt.

First 3 days - 3 oz. M-C mixt. every hour from 7 A. M. to 7 P. M.

After 3 days - (a) A soft egg or a piece of toast is added to one forenoon feeding. (b) Three oz. weighed after cooking, of well cooked oatmeal, rice, or farina is added to an afternoon feeding.

Egg and cereal are gradually added so that by the end of the first week, the schedule is: (a) Three oz. M-C mixt. every hour 7 A. M. to 7 P. M. (b) At the 10 A. M., noon, and 2 P. M. feeding, add a soft egg. (c) At the 11 A. M., 1 and 3 P. M. feeding add 3 oz. cereal. (d) Custards, cream soups, and vegetable purees may at times be substituted for the M-C mixt.

After the fourth week, the patient leaves the hos-

pital and goes on the routine which is to be followed for at least one year; it is detailed below.

3. Alkaline Medication. Two powders are made up:

I. Rx

Heavy calcined magnesia	gr. X	0.6 gm.
Sodium bicarbonate	gr. X	0.6 gm.

II. Rx

Calcium carbonate	gr. X	0.6 gm.
Sodium bicarbonate	gr. XXX	2.0 gm.

For the first weeks of treatment powder no. I is given with every feeding of the M-C mixt. 7 A. M. to 7 P. M.

Powder no. II is taken every hour between feedings; that is 7:30, 8:30, 9:30 A. M., etc.

After the 7 P. M. feeding one of these powders is given every half hour for 4 or 5 doses.

4. Aspiration of the stomach contents is done two afternoons and three evenings of each week until the physician is satisfied that there is no gastric residue and that the acidity is completely neutralized. At first the evening aspiration should be done one-half hour after the last powder is taken, that is at 9:30 P. M. If much secretion is found, powder II should be taken again at 10:30 P. M. and 11 P. M. and another aspiration done at 11:30 P. M. If this aspiration shows considerable secretion (20 c.c. can be considered normal) the powders should be continued every hour all night for a few nights. If it is normal, the powders should be continued to 11 P. M. When the 9:30 aspiration shows a nor-

mal amount of secretion and acidity on several consecutive occasions, the aspirations can be stopped as a routine, and done only for observation once a week or once every two weeks, and the night powders can be omitted.

Routine Treatment after the Fourth Week:- This should be continued for at least one year.

Three small meals daily with M-C mixt. at hourly intervals, and powder on the half hour. The total bulk of any one meal should not be more than 10 to 15 ounces. The character of the meal has been indicated above: eggs, toast, cream soups, mashed potatoes, spinach, soft cooked tomatoes, cooked fruits, custards, cereals, gelatin, whipped cream desserts, milk toast. Meat and meat broths interfere with stool analysis for blood. They should not be given for four days preceding such a test.

After breakfast a powder should be taken every half hour for two or three doses, then about 10 A. M. 3 oz. of the M-C mixture. Half an hour later a powder, M-C mixture and powder alternating every half hour until noon. After the noon meal a powder every half hour for 3 doses, then M-C mixture and powder alternating every half hour. The evening meal should be small, 8 to 10 oz. After supper a powder every half hour for four or five hours.

Aspirations should be done once a month at least. If

the tube shows the stomach empty half an hour after the last powder, aspirations need not be done oftener than once a month.

Now and then the patient can take a regular meal to vary the monotony.

All powders should be stopped for five days at the end of the tenth week. Thereafter every six weeks, the powders must be stopped for five or six days.

Wosika and Emery (86) undertook to determine how often the unmodified Sippy regimen brought about complete neutralization of the gastric contents. For this purpose forty-six patients with duodenal ulcer were given the routine Sippy treatment. Specimens of gastric contents were removed, every half hour from 7 A. M. to 7 P. M., and the free and total acidity determined when only milk and cream were given, and on days corresponding to the "first day","seventh day", and "fourth week" procedures of Sippy. A standard dose of alkali was used in each instance at the time specified in the treatment, which was calcium carbonate 0.6 grams and sodium bicarbonate 2 grams. The treatment given abolished symptoms in all cases. The free acidity was adequately controlled in more than one-half of the patients, even though no variations were made in the amount of alkali given. Fifty-four percent were controlled on the "first day", 71 percent

on the "seventh day", and 57 percent on the "fourth week" Sippy. Sippy had formerly recognized the importance of individual variations. The data from this investigation show that if the free acidity does not rise above 20 after an alcohol test meal, the patient will obtain adequate control by this treatment. There seem to be no criteria to determine which patients will be controlled in the larger group whose free acidity goes above 20 following an alcohol test meal. The data also indicate that the addition of alkali to hourly feedings of milk and cream in the amount given, produces but little decrease in free acid. If a routine treatment is used one can be assured of complete neutralization only if frequent aspirations are done.

Since the development and acceptance of the Sippy regimen, there have been many modifications instituted in the practice of various physicians. Such a modification may be said to be any regimen which recognizes the etiological factors of hypersecretion and hyperchlorhydria in the production and maintenance of chronic peptic ulcer, and in which treatment by diet with or without alkalies reduces these factors to a considerable extent. It is still debated today whether complete neutralization of the gastric contents is necessary for good results in treatment. So modifications have been developed; those which allow the patient to remain

ambulatory during treatment, those which continue the diet for less than twelve months, those in which complete neutralization is not necessarily sought, and those in which alkalies are not used. There are many arguments for and against these modifications.

It is quite difficult to evaluate the merit of different treatments because of the natural remissions which are characteristic of the condition, the many factors probably contributory to its development and continuation, the long follow-up period necessary for accurate evaluation, and the large amount of time and expense necessary for radiographic check-up. Most authors today agree that medical treatment does not expect to permanently cure an ulcer patient but simply to produce a remission of symptoms and healing of the ulceration, and attempt to prevent relapses. Most statistics compiled over a long period of time show that most patients have one to many relapses after a recognized healing of the ulcer. This simply means that any immediate medical treatment that will completely heal a peptic ulcer is as valuable as any other temporary treatment which completely heals the ulcer, as far as the likelihood of recurrences is concerned. It is therefore of highest importance to advise the patient concerning the prophylaxis against relapses. For this reason less strenuous treatments

for the patient have been devised which have likewise met with various degrees of success.

Alvarez (49) felt that the strenuous regimen of Sippy was not necessary in the treatment of most uncomplicated peptic ulcer cases. He permits the patient to remain at work and advises as the basis of treatment three good meals daily with feedings at stated intervals between times. The food for the meals is chosen from his "Smooth Diet" list. For the between feedings a mixture containing a quart of milk, two eggs, and perhaps a half pint of cream is placed in a thermos bottle, which the patient takes with him to work. If milk is not well borne, thin cereal gruels may be substituted. Assuming that the patient eats three good meals daily, at 7:30 A. M., 12 and 6 P. M., he then takes between meals at 10 A. M. and 2, 4, 8, and 10 P. M. a glassful of the milk and egg mixture. Another glassful may be taken if he awakens during the night. If this mixture is not available, a milk shake or malted milk at the soda fountain may be substituted.

For patients whose pain is likely to recur within a short time, say an hour and a half, Alvarez advises that a different schedule be substituted, and that they take the mixture at intervals of one and one-fourth hours. He feels, however, that severe cases such as these as a rule demand surgical treatment.

The patients are asked to do as little hard work as possible, and are told especially to refrain from lifting, gardening, "the daily dozen" and even golf. Walking is the only exercise encouraged.

Alvarez has seen prompt relief follow the institution of this regimen, and he believes that by means of it the majority of patients will in the course of time apparently be cured, although he uses the word "cure" cautiously. He insists that they observe these directions for six months or a year, and that they continue always to take some food between the regular meals.

According to Emery and Monroe (26), statistics based on a study of 1,435 cases showed that 90 percent of the patients treated on the Sippy regimen obtained a satisfactory result as compared to a modified or partial Sippy (such as the Alvarez treatment) in which 87 percent were satisfactory. For this reason these men have abandoned the Sippy regimen in most uncomplicated cases, especially if it is any hardship to the patient. They state that the proper use of alkalies lies chiefly in the relief of pain in the early stage of treatment but that they do not promote healing unless there is complete neutralization, to which Sippy also agreed. It is their belief that the use of alkalies should be discouraged as far as possible to

prevent patients relying on them to the neglect of other measures which do promote healing.

Among other authors recording satisfactory results with ambulatory treatment are Davies (22) and Bassler (6).

Palmer (61) states that frequently it seems impossible to obtain satisfactory control of the free acidity even with large doses of alkalies in the Sippy regimen. In spite of this fact he feels that conservative medical therapy based on the principle of acid neutralization remains the treatment of choice for uncomplicated peptic ulcer.

Hill (36) states that he usually institutes first the ambulatory treatment with diet and alkalies. If this is unsuccessful, the patient is given bed rest with the Sippy regimen and upon the success or failure of this hinges the need for surgical treatment.

Dowden (23) writes an opinion similar to this.

Alkalosis and Generalized Effects of Alkalies

Since the wide acceptance of the Sippy regimen in this country, there have been appearing in the literature rather frequently, reports of alkalosis in patients following this treatment. According to Jeghers and Lerner (40) the following mechanisms may be responsible for the development of such an alkalosis and the clinical course is determined by the degree and number of factors present.

1. Loss of gastric juice. The chloride is lost leaving a relative excess of basic radicles. The carbon dioxide combines with them to form bicarbonates and the carbon dioxide combining power of the blood is increased.
2. Pre-existing renal disease.
3. Hyperalkalinization.
4. Insufficient chloride intake. The normal intake is from ten to fifteen grams per day. The usual ulcer diet contains about 2 grams.
5. Hemorrhage. Only contributory through chloride lost.
6. Anemia. Experience has shown that severe anemia predisposes to the development of alkalosis.
7. Impaired liver function. The liver is important in maintaining acid-base equilibrium. Patients with cirrhosis cannot tolerate either acids or bases well.
8. Warm weather. More chlorides and fluids are lost.

Usually several factors must br present before symptoms appear.

The typical clinical manifestations of this type of alkalosis (18) are as follows. The patient begins to suffer from a feeling of tiredness with impairment of mental ef-

ficiency and powers of concentration. The onset may be insidious or rapid. This mental lethargy increases in intensity and soon becomes associated with definite changes in the personality, with irritability and unreasonableness, and finally definite drowsiness or even coma. Mental change is the most striking manifestation of this type of alkalosis. During the onset of the mental change vomiting usually occurs. Headaches and generalized muscle pains may be complained of, and conjunctivitis not infrequently develops with sore and red eyes. Tetany, either manifest or latent, appears to be unusual.

The following changes in the urine and blood may be noted.

Changes in the urine.

1. Increase in the amount, often over three liters a day.
2. Concentration of urea low and chlorides almost completely absent. Low chloride concentration may be a valuable aid in diagnosis.
3. Albumin present in small but definite amounts. Hyaline and granular casts are usually present.
4. Usually alkaline and effervesces on the addition of acid because of the high bicarbonate content.

Changes in the blood.

1. Those typical of uncompensated alkalosis.

(a) Raised P^H.

(b) High plasma bicarbonate and low plasma chloride, the rise in the former approximately balancing the fall of the latter.

2. Those referrable to seriously impaired renal function.

(a) High blood urea and N. P. N.

(b) High plasma creatinine.

(c) Raised plasma phosphate.

The finding of a raised blood urea is an extremely valuable point in diagnosis and when present in a patient with gastric ulcer who is showing suspicious symptoms and who has no history or evidence of previous renal disease, it is practically diagnostic.

Magnesium content of the blood rises when its introduction into the body is pushed, especially when there is some renal damage as in alkalotics. This is important in two ways: (a) it has a sedative action which tends to overcome the tetanus of alkalosis, and (b) it may well account for at least some of the mental symptoms.

Renal damage recovers only after two to four weeks after the alkalies have been withdrawn.

Berger and Binger (9) reported seven cases of alkalosis which were due to the administration of alkali in peptic

ulcer. Evidence of impaired renal function was found in five cases after the alkalosis had been rectified. They felt that previously impaired renal function is an important etiologic factor in alkalosis and that it should be considered in the treatment of peptic ulcer with alkali.

In any suspected case of this type of alkalosis, according to Oakley (58), all alkalies should be suspended and the alkali reserve and blood-urea estimated without delay. If these are raised, acid should be given in the form of ammonium chloride and sodium phosphate, the former in the dose of 15 to 20 grains and the latter 30 to 40 grains, three times daily after food until the alkali reserve, which should be estimated daily, or at least every two days, has returned to normal limits. The protein intake should be limited to about 40 grams a day, and all food given in fluid or semi-fluid form, careful attention being paid to the condition of the mouth and bowels.

UTILIZATION OF DIETARY IRON:- Another point to be borne in mind when putting a patient on alkaline therapy is the effect of alkalinizing the gastro-intestinal tract on the utilization of dietary iron. Kellog and Mettier (43) noted, in peptic ulcer patients anemic from hemorrhage, that the bone marrow failed to respond to the ingestion of dietary iron while the patients were undergoing the alkaline

therapy of a modified Sippy regimen, but that on withdrawl of the alkaline regimen an increase in the concentration of hemoglobin occurred. In contrast, increases in the number of erythrocytes and reticulocytes occurred soon after the addition of the iron-rich diet to the alkaline regimen. It is concluded that alkalinization of the upper part of the gastro-intestinal tract interferes with the utilization of dietary iron for the synthesis of hemoglobin but not with the utilization of material necessary for the formation of erythrocytic stroma.

VITAMINE DEFICIENCY:- Without paying particular attention to guard against avitaminosis in patients on the Lenhartz or Sippy regimen, it is quite easy for this condition (2) to develop. These diets are deficient in vitamine C. It has been noticed that in doing surgery on ulcer patients long on an ulcer diet, that the wound is apt to heal poorly. It has long been known that wounds heal poorly in scurvy and it may be that these facts bear to each other a cause and effect relationship.

It has been shown in experiments on rats and guinea pigs that ulcers of the stomach and duodenum are liable to develop when animals are in a subscurvy state. At present it is impossible to say if ulcers in man may develop because of a subscurvy state, and it is difficult to say whether

ulcers heal faster when the patient is saturated with vitamine C or ascorbic acid. However, that six out of nine patients with gastric and duodenal ulcers are in the subscurvy state, coupled with the knowledge that the diet of milk, eggs, bread, and butter contains very little ascorbic acid, is sufficiently strong evidence to advocate the use of adequate amounts of ascorbic acid in the treatment of these conditions. Two ounces of orange juice will supply 36 milligrams of this substance, and giving such a dose every day will prevent the "subscurvy"state from developing further. It is preferrable to give a dose of 1000 milligrams in the form of ascorbic acid on three successive days, as this insures the saturation of the system with it, and then continue giving 36 milligrams daily in the form of orange juice. If the patient has an obstruction of the pylorus, which is causing vomiting, the ascorbic acid may be given intravenously.

Platt (63) reported three cases of peptic ulcer who had been on a limited diet and who were true examples of clinical scurvy. The scurvy cleared up in a short time after administration of the proper vitamine.

Use of Milk in Other than the Fresh Form

Davidson, Biguria, and Guild (21) have conducted a series of experiments which seem to indicate that evaporated

milk, diluted or undiluted, may be used as well as milk, and milk and cream mixtures, in the treatment of conditions that require a bland or semi-bland diet, so far as its influence on gastric acidity and motility are concerned.

Wosika and Emery (86 -87) found that 12.5 grams of a preparation of powdered whole milk mixed with the usual Sippy powder, 0.6 grams of calcium carbonate and 2 grams of sodium bicarbonate, and given at one hour intervals with 3 ounces of water, is somewhat more effective in neutralizing the gastric acidity than 3 ounces of milk and cream (20 per cent) and the same powder given in the usual way advised by Sippy.

The following explanations are given for these results. The flavor may be involved. The alkalinized milk powder has a flatter and more unpleasant taste than the regular milk and cream mixture and may not, therefore, cause as much psychic secretion. There is a greater amount of protein in the powdered milk which should decrease the amount of free acid by increasing the neutralization. The powdered milk provides one-fifth more protein than the milk and cream. The curds of the powdered milk are smaller which allows the protein to act more effectively in neutralizing the acid.

The advantages for this type of medication are: (a) the patient needs to carry only one mixture instead of two,

(b) medication is necessary only one-half as often, and (c) the cost is somewhat less if unadvertised powdered milk is used.

The disadvantages are: (a) the disagreeable taste, and (b) some difficulty in mixing.

More recently the alkali and powdered milk have been put up in tablets. These give slightly less alkalinization than the powder form but still considerably better neutralization than the Sippy regimen, even though the patients using the tablets are ambulatory. The tablets are very convenient to carry and take between meals.

CONTINUOUS NEUTRALIZATION METHODS

It has been previously stated that great difficulty is sometimes encountered in maintaining gastric neutralization in peptic ulcer patients. This is particularly true at night when using the usual methods. Winkelstein (83) studied the gastric secretion curve in 169 cases to ascertain the problem of neutralization at night. He found that normal individuals have little or no free hydrochloric acid at night. Patients with duodenal, gastric, and jejunal ulcer were found to have a high nocturnal curve and high titer of hydrochloric acid. It is not known whether this is cause or effect. He found that nocturnal hypersecretion and hyperchlorhydria could not be controlled by alkalies, olive oil,

atropine, and aspiration when done at 7 P. M. in 75 per cent of cases. In this authors opinion the best medical method of controlling the gastric secretion during the night is by the continuous milk drip. Surgically, partial gastrectomy frequently accomplishes the same result.

Winkelstein (82) proposed the following method of gastric control by the continuous alkalinized milk drip. The mixture used is five grams of sodium bicarbonate to the quart of milk. This drips through a stomach tube at the rate of thirty drops a minute. This amounts in one day, to three quarts of milk and fifteen grams of sodium bicarbonate. This is continued twenty-four hours a day for two to three weeks and then only at night, while during the day feedings are given every one to two hours with alkalies and atropine between. The patient is dismissed after four weeks.

The author treated 42 patients in this way and among the features of these cases worthy of comment are the following. (a) The loss of all symptoms in 4 to 6 hours after the institution of the drip. (b) The complete comfort (including excellent sleep) of almost all the patients while on the drip. (c) The eagerness to return to the drip on the recurrence of even slight symptoms. (d) In several instances where no relief was obtained from the Sippy or mucin treatment, immediate improvement followed the drip treatment. (e)

In many instances disappearance of the radiographic signs of the ulcer. (f) Although the subsequent course was not long enough to justify a conclusion, with one exception, no definite recurrences were noted. The patients were observed from 3 months to 3 years. (g) The willingness on the part of several of the patients to continue the drip at night at home, thus continuing an ideal ulcer therapy for long periods while pursuing their ordinary daily occupations.

One should, however, point out the following to temper the above. (a) The method is somewhat inconvenient to the patient. (b) It is not an ambulatory method. (c) One must consider the striking tendency of ulcer to recur after any form of medical therapy. (d) The probable intolerance of some patients to milk. (e) A larger series of cases and a longer follow-up study is necessary before drawing definite conclusions.

FEEDING BY INTUBATION

Maile (51) reported on 25 patients treated by duodenal intubation. The tubes were left in place and used for all feedings. The author aimed at 2000 calories a day and divided this into 8 feedings, giving one every two hours during the day. The feeding best tolerated was milk eight ounces, glucose one dram, one-half egg, and haliver oil

three minims. The author felt that soya beans would be an ideal food in this condition when the fresh beans are available, with eight ounces of soya bean soup made with milk, serving as an alternate feed with one of milk eight ounces, glucose two drams, one egg, and haliver oil three minims. The patients were soon able to feed themselves and the large loss of weight sometimes observed in ordinary medical treatment did not occur in these cases. The following are observations by the author concerning this method of treatment. (a) The patient was confined to bed for only one week instead of three or longer. (b) In all cases of severe pain, there was complete relief immediately after intubation. (c) After eight months only one case had a return of symptoms, and this was a very long standing case of gastric ulcer in which gastroenterostomy had to be done. (d) In two cases of severe hematemesis, the ability to feed the patients immediately appeared to overcome their debility from loss of blood.

In this man's experience, this method of treatment has many advantages over the ordinary routine treatment of bed, milk, and alkaline powder.

Bourne (11) has made a study of the treatment of peptic ulcer by duodenal feeding. He feels that by this treatment, as compared with the Lenhartz diet, gastric ulcers heal on an average of a week sooner, and that the diet is simpler,

has more calories, and can be varied to the need of the patient. For duodenal ulcers the author finds the results the same and has reverted to the Lenhartz diet.

Physiologists have shown by the "balloon method" that feeding with the jejunal tube causes no peristaltic waves in the stomach. It has also been shown that there is no increased acid secretion in the stomach when food is taken in this way. These facts formed the rationale for jejunal feeding of gastric ulcer patients by Gilgas and Weber (33). The mixture used was one quart of milk, two ounces of sugar, two ounces wheaten flour, and two ounces of butter. Five two six ounces of this mixture at body temperature were injected slowly through a nasal tube every two hours with a syringe. After four weeks an x-ray was taken and if the ulcer showed healing, the next three days a little milk was given by mouth but most of the nourishment still by tube. The tube was then withdrawn and a light diet suitable for gastric ulcer was given in increasing variety and amount and the patients released in eight to ten days. Gilgas and Weber reported eight gastric ulcer cases treated in this way. Without exception the patients, after this treatment, were free from pain and signs of indigestion, gaining in weight, and feeling well. Radiographically, the ulcer disappeared in six, was much smaller in one, and

unchanged in one. The authors feel that this method will give better results with gastric ulcer patients than ordinary treatment, and that it should be tried especially in those cases in which previous treatment has been more or less unsatisfactory.

COLLOIDAL ALUMINUM HYDROXIDE

In 1934 Einsel, Adams, and Meyers (24-25) reported one hundred and ten cases of peptic ulcer which they had treated, using colloidal aluminum hydroxide as an antacid, only eight percent of which had poor results. In a report in 1936 their series had risen to one hundred and twenty-five cases. The treatment consisted of a modified Sippy convalescent diet with six feedings a day, followed by four to twelve c.c. of gelatinous aluminum hydroxide one-half to one hour after the ingestion of the food. The patients were ambulatory and were allowed to resume work after two or three weeks if it was not too strenuous.

One c.c. of the aluminum hydroxide neutralizes twenty c.c. of 0.1 normal hydrochloric acid in four hours. The neutralization is characterized by a rapid partial neutralization followed by a slow reaction until the endpoint is reached.

The conclusions of these investigators concerning this

antacid are as follows. (a) Symptoms of peptic ulcer rapidly are brought under control--usually 2 to 7 days. (b) Since the treatment is easily followed, it quickly gains the patient's confidence. (c) No toxic symptoms observed in any case. (d) Free acidity of the stomach is lowered after treatment with aluminum hydroxide, but returns to the initial level after the medication is discontinued. In contrast to sodium bicarbonate, aluminun hydroxide does not stimulate an increase of hydrochloric acid output after its primary action. (e) Although aluminum hydroxide obviously serves as a gastric antacid, it is possible that its efficacy in the treatment of peptic ulcer may be dependent in part, at least, upon its slight astringent and demulcent properties and the fact that it appears to increase the secretion of mucin. (f) No contraindications for aluminum hydroxide therapy have been observed. (g) This drug appears to be the antacid par excellance.

Woldman and Rowland (84) have used 7 percent aluminum hydroxide as a continuous drip in the treatment of peptic ulcer. They state that it acts mainly by adsorption and that chemical union is at a minimum. With heat and concentration, chemical union proceeds more rapidly. Blood analysis shows no appreciable change in the blood after large doses.

A small Levine tube, size 12, is passed through the nostril to the stomach. The mixture used is 200 c.c. of 7 percent aluminum hydroxide and 600 c.c. distilled water. It is allowed to enter the stomach at the rate of 5 to 6 drops a minute. At this rate 800 c.c. lasts twenty-four hours. Samples may be aspirated at any time for analysis.

This treatment gave prompt relief from pain, especially night pain, which was one of the striking results. A constant achlorhydria was produced as proved by frequent sampling during the day and evening and before the morning feeding. Both gastric and duodenal lesions, quite apparent in the x-ray films, practically disappeared in 7 to 14 days. One recent case with a definite niche had had persistent pain for 4 weeks in bed on the Sippy routine. Operation was advised but aluminum hydroxide drip was tried as a last resort. Within one week all pain was gone and x-ray at the end of 7 days failed to show the niche.

If reliance is to be placed on antacid treatment, there is every reason to carry it out in the most thorough and continuous manner. The continuous 24 hour aluminum hydroxide drip is free from danger of alkalosis and of secondary acid secretion. The method is entirely compatible with any type of dietetic or sedative treatment. Because of the continuous neutralization, the diet can be suited more definitely to

the nutritional needs of the patient rather than having crowded in frequent feedings to control acidity and often with a great excess of fat, with its metabolic disadvantages. Functional rest of both the secretory and motor function of the stomach may be allowed in a larger measure during the period of healing. Three or four small bland feedings a day are sufficient, such as milk, one-third cream, junket, custard, jello, and a cereal including the protective foods and vitamines.

Many cases of ulcer occur in well nourished or over weight people. Warncke reported 83 percent of 523 cases to be moderately well or extremely well nourished and only 16 percent in a poor state of nutrition. With the former a limited diet may be used during the aluminum hydroxide drip treatment to get prompt control of the active stage of ulcer. Especially for the intractable case, before surgery is resorted to, this method represents an additional refinement of technique in medical management.

DIRECT TREATMENT

Cash (16) treats peptic ulcers by direct treatment. He makes the following points concerning this treatment. It consists of repeated irrigations, and suction with the tube. Ulcer treatment requires building up of the resisting power of the tissues, from which new granulation must come. The

original cause and the chronicity of the disease have lowered the ability of the tissues to form granulation as well as their power of resistance against the chemical and mechanical factors resulting from their location. Ability to regenerate is further lowered since the vitality of the tissues has been dissipated in defense in old lesions. Cleansing the lesion is a first essential, to be followed by applications. In a similar lesion on the external surface of the body this form of treatment would be applied. Other medical treatments lack these features.

Exudate is closely adherent even in shallow ulcers. It rapidly reforms. Medication by mouth without removal of the exudate cannot reach the base of the ulcer. After the lesion has been thoroughly cleansed with resulting stimulation, medication is applied directly through the tube. Silver preparations are used; collene, six drams of one-half to full strength, is applied gradually over a ten to twenty mihute period, after which the tube is removed. Collene is astringent and stimulating. It is applied routinely in the early and active stages. After the slough and bleeding have disappeared and in indolent ulcers, silver nitrate one-sixtieth of one percent in solution or weaker may be substituted at interwals. A solution of tincture of iodine, two or three drops to the ounce of water, also stimulates granulation.

Tube treatment is given once or twice daily, depending on the amount and type of exudate and the rapidity with which it reforms. Medication may be forced in to reach all parts of the lesion. Care and judgment are obviously necessary in the initial tests and in treatment where bleeding is present or penetration has been proved with the x-ray or is suspected. Free bleeding requires mild or no suction but collene is applied several times daily until it has diminished or ceased.

Direct treatment definitely, often rapidly, diminishes the exudate. Improvement in the general condition and symptoms parallel its disappearance, while tube returns furnish visual evidence of progress. Suction, irrigation and applications are also used in chronic ulcers without exudate, that is, the indolent, and those in a state of granulation.

Obviously rest in bed, diet, antispasm, alkaline and other indicated medication are required. Contrary to the theory that complete neutralization of hydrochloric acid is necessary, it was not done in any of the author's cases. A moderate dosage of alkaline powder was given as a routine. In supersecretion and to relieve pain, alkalies were given more freely.

None of the routine diets are given. Fasting, beginning of feeding, quantity and quality of food are controlled

chiefly by the tube returns. This removes haphazard guessing. Transduodenal feedings may be given with treatments by passing the tube beyond the ulcer. When a feeding is finished the tube is drawn up the required measured distance to the ulcer and treatment applied. They are only given when indicated.

In both acute and chronic ulcers bed treatment is indicated. It is a positive aid to recovery in all peptic ulcers according to this author. The average time requied to heal chronic gastric or duodenal ulcers with the direct method is four to six weeks, if the patient is placed in bed. Stage, size, depth and location of the lesion obviously influence the time. All gastric ulcers heal readily. Chronic ducdenal ulcers may heal in the average period but if associated with severe pyloric spasm with or without hypertrophy, healing may be delayed.

MUCIN

From 1931 to the present there have been a considerable number of articles published on the use of gastric mucin in the treatment of peptic ulcer.

According to Fogelson (29) certain physiological observations suggested the use of gastric mucous as an ideal antacid in that (a) it combines readily with free acid, (b) it is a natural substance which plays normally a protective,

soothing, and lubricating role in the functioning of mucous membranes, and (c) its secretion or ingestion causes no chemical disturbances in the body and no unfavorable effect on the gastro-intestinal secretory or motor activity.

Whitlow, studying the protective role of gastric mucus against the proteolytic action of gastric secretion, concluded the following. Gastric mucus delays and inhibits, though does not prevent, the diffusion of hydrochloric acid and pepsin. The rate of diffusion of hydrochloric acid through gastric mucus is inversely proportional to the depth of mucous layer and inversely proportional to increase in viscosity of the mucus; the diffusion of pepsin is directly proportional to the time required for the hydrochloric acid to diffuse through the entire depth of the mucous layer. The presence of tenth normal hydrochloric acid in gastric mucus hastens the rate of diffusion of pepsin through a layer of mucus. The fact that gastric mucus covers the mucous membrane of the stomach with a viscid, tenacious coat that retards digestion and diffusion of gastric juice as shown by in vitro experiments makes it impossible to deny the protective role of this secretion against autodigestion of the stomach. The most direct evidence of all, however, is the fact that when the mucus is wiped away with a cotton swab and tenth normal hydrochloric or normal gastric

juice is applied, bleeding occurs, and when merely swabbed with equal vigor and mechanical irritation, no bleeding occurs. It becomes a self evident fact, therefore, that mucus protects the gastric mucosa against the action of gastric juice.

Similar results are reported by Klug and it is highly probable that the relief from symptoms obtained from feeding the mucin preparation was secondary to two factors. First, the mucin coated the ulcer and protected it against the proteolytic action of the gastric secretion, and second, through its high combining power with free acid it united with enough hydrochloric acid not only to neutralize the corrosive action of gastric juice but also to prolong the rate of dialysis of pepsin through the now present protective mucin layer. Obviously, both these factors would be important in affording relief from pain and in hastening healing.

Fogelson also makes the following additional observations on mucin. He feels that mucin therapy should be preceded and followed, as well as accompanied by, well recognized measures.

Mucin, like other forms of treatment, has its disadvantages. Bloch and Rosenberg (10), in their experience with thirty mucin treated patients found some would not continue its use because of its disagreeable taste and

certain untoward symptoms as intensification of all symptoms, nausea, vomiting, pain, anorexia, flatulence, diarrhea, and cramps. As a result of their experience, however, they advocate its use in cases refractory to other forms of therapy as a step toward the evasion of a surgical procedure.

Mucin is a glucoprotein (31) containing glucuronic acid, known to detoxicate certain substances such as phenol. The toxic substances in question combine with glucuronic acid and are eliminated in the urine as glucuronates. The question whether glucuronic acid is synthesized in the body is disputed. But obviously, if glucuronic acid is not synthesized in the body, and is used excessively for detoxifying purposes, the amount of mucin present would tend to be diminished. It is interesting to note that damage to the liver and gastroduodenal ulcer are frequently associated in the experimental animal. This important phase of mucin chemistry and metabolism is being further investigated.

A study (31) based on questionaires concerning 494 patients with peptic ulcer treated by clinicians throughout the United States has demonstrated the ability of gastric mucin to control all the symptoms in 70.5 per cent and to afford a partial relief of symptoms in 23 per cent, while failure to afford any relief occurred in 6.5 per cent. In 217 patients with intractable ulcers who could not be relieved of symptoms by medical management, of whom 69 had been sub-

mitted to previous surgical procedures, gastric mucin afforded complete relief in 63.1 per cent, partial relief in 29.4 per cent, and no relief in 7.5 per cent. The results obtained in this group of patients with intractable ulcers suggests the possibility of obtaining symptomatic relief with gastric mucin in a relatively high percentage of patients in whom accepted orthodox measures, including operation, have failed. The permanence of the results, however, is not considered, owing to the limited period of observation.

In 1932 Rivers, Vanzant, and Essex (68) reported the demonstration in certain specimens of commercial mucin the presence of large amounts of a secretogogue which by biologic tests seemed to be histamine. The presence of this substance may be looked upon as a contaminant which can be avoided if proper methods of preparation are used. Since that time the refinement in preparation has eliminated much of the secretogogue action of mucin.

In 1933 Rivers and Vanzant (66) reported 150 cases of peptic ulcer treated with mucin, only 50 per cent of which responded favorably. They do not feel that it is an adequate substitute for other approved methods of treatment.

These authors (67) state that ordinarily, if patients have uncomplicated peptic ulcer the use of 100 grams of mucin

(seventy per cent protein) daily does not cause changes in the value for blood urea. Its use, however, in patients having ulcer and associated advanced hepatic or renal disease, should be carried on with caution, because untoward symptoms may develop during the course of treatment. It has been the custom of these men, when such complications exist, to use smaller amounts of alkalies and mucin in order to accomplish reduction of acidity. Apparently, such patients get along very well on this modified type of treatment.

The specific cause of untoward effects produced in certain cases with marked hepatic or renal disease has not been determined, although it is possible that the protein factor alone or some protein derivative is the cause.

It is reported that in 1934 mucin prepared from the mucous membrane of hog's stomach was brought before the Council on Pharmacy and Chemistry of the American Medical Association (1) for its consideration and approval. It appears that, although the early studies with mucin treatment indicated ~~indicated~~ beneficial results in a fairly large number of patients with peptic ulcer that had failed to respond to other methods of treatment, later publications have emphasized that there are limitations to this form of therapy. Gastric mucin is a viscid, unpalatable preparation and many patients refuse to continue treatment; nevertheless, the

product appears to be of value in a number of patients that have not done well on usual ulcer therapy. For these reasons the Council decided to postpone at that time further consideration of the preparation pending the accumulation of additional evidence as to its therapeutic usefulness.

OKRA

Because of certain disadvantages in the use of mucin, such as its unpleasant taste, secretogogue action, and being an animal product, subject to decomposition and putrefaction, it was attempted (5) to find a vegetable substance which would have a rich yield of mucilaginous material and contain glycuronic acid. Among the plants studied, the pod of the okra plant seemed most suitable. The mucilaginous material was extracted from the pods and converted into a fine powder which was called "okrin". This material was entirely free of secretogogues when tested on a dog with a pouch of the entire stomach.

Neckels, Sapoznick, Arens, and Meyer (57) tested the effects of hog's mucin, okra, olive oil, and agar on the motility of and the digestion in the stomach. Tests were performed on six normal subjects, on six patients affected with peptic ulcer, and on a dog carrying both gastric and duodenal cannulas. While all of the test substances decreased the

emptying time of the stomach, okra had the greatest effect. At the beginning of digestion, hog's mucin increases and okra decreases gastric motility. After three hours, this is reversed, and okra diminishes the emptying time by 26 per cent. In the stomach okra does not impair the digestion of meat; it considerably decreases the amount of gastric secretion.

It is difficult to say how a delay in emptying time benefits an ulcer patient. Perhaps in such circumstances the food proteins can bind more of the secreted acid and soft food may protect the mucosa during the mixing process. The shortened emptying time in the third hour and the decrease in the total amount of secretion as well as the complete digestion of meat, may explain the favorable effect of okra in some cases of peptic ulcer. Although okra increases the acidity of the stomach contents, nevertheless, in view of the decreased volume of total secretion, the acid may be neutralized more easily by mucus, regurgitation from the duodenum, and food in the stomach: thus it is quite possible that one effect neutralizes or overneutralizes the other. This initial delay of emptying time after okra may be beneficial also by allowing the stomach to remain filled while the intestinal phase of gastric secretion is beginning, so that the acid secreted then can be bound by the buffers of the

food. It would seem logical to assume that okra would have its optimum effect when it is given simultaneously with the meals of a proper diet.

An increased acid response to okra was found (55) in 72 per cent of ulcer patients and 50 per cent of normal students studied. This suggests a striking similarity to results obtained on using impure mucin. Whether okra contains a histamine-like substance was yet to be studied.

The relief of symptoms despite an active acid response in a great number of these patients may seem at first difficult to interpret. It has been shown that the pain of gastric ulcer is independent of acid secretion. It may be that the associated gastritis is the principle cause of pain. It is quite likely that the okra relieves the symptoms by alleviating this gastritis and duodenitis.

Meyer, Seidmon, and Neckeles (55) reported the treatment of seventeen patients with tablets of powdered okra. Fourteen of these patients had immediate relief of symptoms. Early withdrawal of the tablets caused a recurrence of the symptoms which again disappeared with more tablets, which shows that it was the okra controlling the symptoms. The treatment consisted of a one-gram tablet of okra every two hours. If there was distress at night two tablets were given at midnight or early in the morning or both. The

authors emphasize that this study merely indicates the value of this preparation in relieving ulcer symptoms and not as a cure since their patients had not been watched sufficiently long after treatment.

For two years Atkinson (5) studied 22 selected ulcer patients who were being treated with okrin. Patients in a gastro-intestinal clinic having the most difficulty on other managements were chosen. This method of selection of patients attempted to eliminate that large percentage of ulcer patients which has temporary remissions after any type of treatment. All patients had history, signs, symptoms, laboratory evidence and roentgen manifestations of peptic ulcer. Ewald test meals, fractional and motor test meals and examination of stools for occult blood were performed. This series included one patient affected with a prepyloric ulcer, eight who previously had had gastro-enterostomy performed with recurrent lesions at the stoma or in the duodenal bulb or both, and thirteen with duodenal ulcers. Some had the complication of gastric retention and a definite continuous secretion as evidenced by retention and night distress. The chronicity of the ulcer diathesis was indicated by the 4.2 years average duration of periodic pain.

Treatment consisted of four to eight grams of okrin taken in water, milk, canned milk, or milk and cream every

hour while the patient was awake. Most patients were allowed three smooth, bland, low secretogogue-yielding meals daily, with adequate vitamins and minerals, but if there was marked retention or vomiting, feedings were begun gradually. All patients were treated while ambulatory.

In seventeen of the twenty-two patients remission occurred in from one to ten days. There was an absence of pain during the day, a cessation of vomiting and pyrosis, and diminution of night distress within the first two or three days. During the next two weeks there was a disappearance of the night distress, of epigastric tenderness and of blood from the feces. Re-examination gave roentgenographic evidence of decreased pylorospasm and decreased emptying time. It was not possible to give a definite opinion of anatomical changes in the lesions except in those prepyloric ulcers with niche formation which roentgen anomaly disappeared after treatment. Three patients with duodenal ulcer and two with jejunal ulcers failed to obtain relief. Some of the failures in this "intractable" group might have had complicated ulcers with accompanying perigastritis or periduodenitis and peritoneal adhesions causing pain. There is also the possibility that cicatrized ulcer was the cause of continuous discomfort along with

gradually increasing stenosis due to cicatricial contraction and fibrous connective tissue thickening at the border of the ulcer. Ten patients after preliminary treatment did not take okrin for periods of from one to six months. Three of these had recrudescences which again were relieved by okrin.

This study indicates that okrin relieves pain in patients with peptic ulcer and apparently produces a remission in a large percentage of ulcer-bearing individuals. It cannot be proved that the ulcers were healed, but the rapid relief of pain indicated a subsidence of accompanying gastritis and duodenitis.

A direct comparison of the benefit of okrin with gastric mucin cannot be made in a disease whose natural history is so variable. It was the author's impression that patients taking okrin did not gain in weight so rapidly as those taking mucin.

Okrin is pleasant to take and produces no untoward symptoms. It does not deteriorate or putrefy. It apparently has a palliative, demulcent action and should be considered, according to Atkinson, as an adjuvant to other previously proved methods of treating the peptic ulcer patients' general condition.

INJECTION TREATMENT OF PEPTIC ULCER

Because a certain small percentage of patients suffering from peptic ulcer have always been unable to obtain relief from their symptoms, the medical profession has remained alert for the development of new modes of treatment which might give added relief to these patients. So it is that certain substances have been injected parenterally and intravenously into these patients in the hope that more satisfactory treatment might result.

Histidine

In the past few years much attention has been given to the relatively new histidine treatment of peptic ulcer. Its development evolved from a number of very pertinent experimental observations which have been reviewed by Sandweiss (71).

Exalto was the first to produce peptic ulcers in dogs identical with those observed in man. His experiments, however, were few and his work was unrecognized for years until Mann and Bollman reported a large series of experiments and described the operation (usually described as surgical drainage of the duodenum) and results as follows.

The pylorus was sectioned and the distal end inverted, the jejunum was transected a few centimeters distal to the ligament of Treitz, the distal end was anastomosed to the

pylorus, and the proximal end was anastomosed to the ileum from 30 to 60 centimeters from the termination of the latter. These procedures caused the gastric contents to be expelled from the stomach into the jejunum without becoming mixed with the secretions poured into the duodenum (the bile, the pancreatic juice and the duodenal juice) which are drained into the ileum. Furthermore, the possible protective mechanism of the duodenal mucosa was eliminated by the substitution of the jejunal mucosa. This operative procedure was carried out several hundred times and ulcer developed in about 95 per cent of the experiments.

These results have been confirmed by Ivy and Fauley, Morton, Ravdin and Weiss.

Weiss and Aron in reporting their results expressed the opinion that the absence of duodenal juice affects especially the digestion of proteins. The proteins arrive in the jejunum as gross polypeptides after the albuminoid molecule has been liberated by the gastric juice but cannot be broken down any further to the assimilable components, the amino acids, because the jejunal secretion is deprived of the pancreatic trypsinogen, which is indispensable to this process. Histidine is thus lacking. They claim that it is oneof the four amino acids which cannot be synthesized by the organism (cystine, lysine and tryptophane, they state, are the other three amino acids).

On the basis of these assumptions, Weiss and Aron repeated the experiments with daily subcutaneous injections of histidine-tryptophan mixture. While two untreated controls died, four dogs receiving such injections daily, although showing effects of denutrition, remained happy and sprightly. There was no blood in the feces. Autopsy on two of the four treated dogs after five weeks, on one after six weeks and on one after ten weeks revealed that the mucous membrane was normal. No ulcers were found.

Later Weiss and Aron repeated the experiments after daily injections of lysine, tryptophan, and histidine. Cystine, the fourth amino acid the organism is unable to synthesize from its own resources, was too difficult to inject. Injections of tryptophan or lysine did not change the evolution of ulcer. Injections of tryptophan and histidine combined or histidine alone did. The dogs became anemic and emaciated but remained in good spirits until they were killed, after a maximal survival permitted for the appearance of ulcerous lesions (five to six weeks). Blood never appeared in the feces and autopsies did not reveal ulcers.

From these observations it was reasoned that ulcers in human individuals suffering from peptic ulcer might be due to a deficiency of histidine. Therefore, histidine, in the form of the monochloride, has been injected into several

series of patients. The observations and conclusions drawn from some of these are here given.

In order to study the comparative value of histidine with an accepted form of therapy, Sandweiss (71) made the following observations on 53 ulcer patients treated with a diet-alkali regimen and forty with histidine.

1. Comparative results on early symptomatic relief. (a) Of the patients treated with diet-alkali, 51 per cent became symptom free and 20.7 per cent were moderately improved (a total of 71.7 per cent of favorable responses). Of the patients treated with histidine, 55 per cent became symptom free and 20 per cent were moderately im proved (a total of 75 per cent of favorable responses). (b) Of 17 patients treated with histidine after the diet-alkali management failed to produce remissions, 52.9 per cent became symptom free and 17.6 per cent moderately improved (a total of 70.6 per cent of favorable responses). (c) Of 9 patients treated with the diet-alkali after histidine failed to produce remissions, 42.8 per cent became symptom free and 28.6 per cent moderately improved (a total of 71.4 per cent favorable responses). (d) By changing from one treatment to another and trying all means at hand, to "tire out the ulcer", 73.5 per cent became symptom free and 13.4 per cent moderately improved (a total of 86.5 per cent of favorable responses). Of the 9 patients

not responding to medical management, 4 had ulcer complications such as myocarditis, hyperthyrcidism, or arteriosclerosis.

2. A follow-up of patients who developed remissions showed that 85 per cent of the patients treated with histidine developed recurrences of ulcer symptoms within six months after treatment; of the patients who developed remissions after the diet-alkali regimen, only 31 per cent returned with ulcer symptoms within six months.

3. Twenty-four consecutive daily injections of histidine are not essential to produce a remission or prolong a symptom free period. If 5 or 6 (at the most 8) consecutive daily histidine injections do not cause complete disappearance of all ulcer discomforts, the hope of producing a remission or of prolonging a symptom-free interval by further histidine injections is negligible, based on this small series of patients.

4. About one-third of seventeen patients showed a slight increase in the acid curve; one-third showed a slight decrease and the remaining one-third showed no change in degree of acidity after histidine injections, clinical improvement or failure to improve did not depend on the resultant gastric acidity curve.

5. Of the 24 patients checked by either roentgen examination or operation after histidine treatment, not one

showed disappearance of the ulcer deformity.

6. Sixteen (40 per cent) of the 40 histidine-treated patients developed mild reactions. Obtaining a reaction does not mean that the patient will become symptom free; nor is it necessary for success in treatment.

The author's conclusions are that the comparative results obtained from the above study do not warrant routine injections of histidine in all ulcer patients. The expense involved, the daily visits to office or clinic, the 24 consecutive intramuscular injections, the mild reactions experienced by an appreciable number of patients, the high percentage of recurrences within 6 months after treatment, and what is more important, the fact that approximately the same percentage of patients respond favorably to the diet-alkali regimen without histidine injections --these speak against the routine use of histidine in ulcer therapy.

Histidine produced remission of ulcer symptoms in 55 per cent of the patients treated. When its administration produced remission of symptoms, it did not prolong the symptom-free interval nor did it prevent recurrences; 85 per cent of the patients who developed remissions returned with ulcer symptoms within 6 months after treatment.

However, histidine may be used as "extra artillery" in

patients not responding to the diet-alkali-antispasmodic management. About 50 per cent of the latter patients may thereby become symptom free and an additional 20 per cent moderately improved.

Love (47) reported on eighteen cases of proved peptic ulcer which received in each case approximately 25 injectionss of histidine parenterally, a restricted diet, occasionally alkali to relieve symptoms, and remained ambulatory. None of the cases had mechanical obstruction, recent bleeding, or suspicion of malignancy. The report is based on observations not exceeding nine months in duration. Nine patients became symptom free and had no remaining radiological evidence of ulcer; three cases were nearly symptomless, but the ulcer remained evident although smaller; four patients obtained considerable relief but the ulcer continued to be present; two cases obtained doubtful relief and the ulcer remained present.

Violini and McLaughlin (79) reported a series of 73 cases. The patients remained ambulatory, received a liberal diet, and were permitted to smoke. In no case was there any local, focal, or general reaction, nor were the symptoms aggravated at any time. The patients tolerated a liberal diet and the symptoms in the majority of cases promptly disappeared. In 80 per cent, the general nutrition improved.

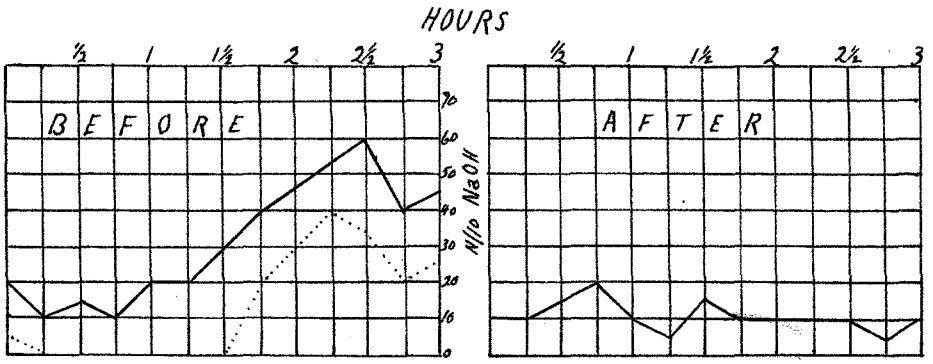
Radiologically, the evidence of healing was greater in cases of gastric than in cases of duodenal ulcer. As a rule, in this series, the percentage of favorable responses varied inversely with the duration of symptoms. Six months after treatment, 79 per cent were reported clinically improved and 21 per cent failures.

Maddox (50) reported a series of 54 patients treated by E. Bulmer with daily injections of 5 c.c. of a 4 per cent solution of histidine monochloride. In some cases the dose was increased to 20 c.c. a day for the entire period of injections without symptoms. No other treatment was given. The results showed that a short ulcer history favored relief from histidine and also that a higher percentage of satisfactory results occurred in the cases of gastric ulcer. In 58 per cent there was immediate success in the treatment, in 19 per cent symptomatic success in which the radiographic evidence of ulcer persisted, and 23 per cent failures. The author feels that the treatment is more applicable to cases of gastric ulcer but that further studies should be observed before making definite conclusions.

Love (48) reported fourteen cases of ulcer proved by x-ray which were treated by histidine. In eleven cases the symptoms disappeared and the ulcer healed radiographically, in one case the symptoms disappeared but the ulcer remained

present, and in two there was no relief as evidenced by symptoms and x-ray.

Gardiner (32) studied the effect of histidine on gastric acidity in twelve patients of which the following are composite graphs. There was a marked reduction in both free and combined acid.



Effect of Histidine on Gastric Acidity

In all of the twelve cases there was relief from symptoms and in every case a fall in gastric acidity. After four to six months, six were still well but in three symptoms had returned.

Because of the prompt symptomatic relief afforded by histidine treatment, (80) emphasis should be placed upon thorough roentgen-ray follow-up in addition to the customary clinical observation.

Wilhelmy and Hashinger (81) treated 26 patients with radiographically confirmed ulcer by the histidine method.

The clinical results of the entire series show 17 cases or 65.4 per cent with complete or partial relief, and 9 cases or 34.6 per cent with no clinical improvement. Of the 17 cases listed under improvement, 13 cases or 50 per cent were completely relieved, and 4 cases or 15.4 per cent were partially relieved.

In this series there were 3 cases in which a Sippy regime would not control the pain, and in none of these 3 cases was the pain relieved by the injection treatment, suggesting, according to this series, the probability of failure of this method in cases which have formerly been intractable under the usual methods of treatment.

Behneman (7) reported a series of seventeen cases, two of which were in shock from hemorrhage, treated by a combination of mucin and histidine therapy. They were given 25 injections of larostidin (histidine hydrochloride), and mucin five times daily, and except for the two in shock, a third-week Sippy diet. In follow-ups six to eighteen months later, it was found that all were symptom free, eight were cured radiographically, and 70 per cent of them were eating everything but roughage, condiments, and alcohol. The author is very enthusiastic about this combined therapy.

Martin (52) in an attempt to determine the relative merit of histidine treatment and diet-alkali treatment,

compared the results of 41 patients treated by the former, and 40 by the latter. The study was carried out as carefully and precisely as possible. The American Medical Association Council on Pharmacy and Chemistry adopted the following report and conclusion in its evaluation of histidine monohydrochloride in the treatment of peptic ulcer.

Immediate and Late Effects from Histidine Treatment in Peptic Ulcer -- Forty-one Cases

	Symptom free			Crater or persistent symptoms		
				Crater		
	Ulcer healed (x-ray)	Ulcer not healed (x-ray)	Total cases	Before treatment	After Treatment	Persistent or recurring symptoms
Immediate results at completion of injections	14	12	30	33	22	11
Late results from 6-12 months	10	3	13	--	--	26
Patients operated on	--	--	--	--	--	4

Immediate and Late Effects from the Diet-Alkali Ambulatory Regimen in Peptic Ulcer -- Forty Cases

	Symptom Free	Crater before treatment	Persistent or recurring symptoms
Immediate results (at end of 4 weeks)	31	35	9
Late results, from 10-12 months	16	--	24
Patients operated on	--	--	3

The symptomatic and radiographic response of the patients in the histidine series was not quite as good as that in the diet-alkali regimen series, in either the initial or sustained effects.

Symptomatic relief with a persistent crater was almost equally common to the two groups, as was a relapse of symptoms. The incidence of relapse was highest in the group rendered asymptomatic but with persistent crater.

Demonstration of a crater establishes a criterion by which a therapeutic substance may be tested, and it also affords a prognostic sign following any form of ulcer therapy. The clinical improvement succeeding histidine hydrochloride therapy in acute peptic ulcer appears to be symptomatic and transient. Chronicity and rhythmicity are characteristic features of peptic ulcer. Histidine appears to have no effect other than to alter rhythm slightly.

Histidine hydrochloride showed no constant effect on the hydrochloric acid secretion in this series. In the quantity used it appears to be harmless.

The therapeutic indications for histidine in the treatment of peptic ulcer are necessarily limited. The extravagant claims that have been made for this substance are unwarranted.

The Council declared Larostidin not acceptable for New and Nonofficial Remedies, because it is marketed with unwarranted therapeutic claims, and voted to postpone further consideration of histidine monohydrochloride until adequate clinical evidence of its therapeutic usefulness is available.

Vaccine and Other Non-specific Protein Therapy

Acute infectious diseases have no predisposing etiologic significance in peptic ulcer, but influenza is definitely known to aggravate the symptoms of ulcer. According to statistics, focal infection has a definite etiologic bearing on peptic ulcer. It is not known just how vaccines act on the patient, but good results have followed their use in the treatment of many of these patients. Suggestions for the mechanism and rationale of the vaccine treatment are (72): (a) Specific desensitization to some unknown organism, (b) diminished acidity after treatment, (c) changes in the vascularity of the ulcer area, and (d) a non-specific action upon the sympathetic nervous systems which in some way influences the nervous control of the ulcer area.

Sandweiss and Meyers (72) treated 33 patients by injections with a stock, polyvalent respiratory vaccine. These patients had not responded to usual diet-alkali management; many of them represented the most intractable cases in a large series of ulcer patients. Treatment was ineffective in 29 per cent of the cases. Remission in symptoms occurred in 71 per cent of the attacks. The duration of the remissions was less than three months in

half the cases benefited. In the remaining half the duration was 4 to 24 months. Patients showing a favorable response were subjected to a prolonged period of follow-up observation. Symptoms recurred in all cases but one, who continued symptom free after 36 months. All patients remained ambulatory and only two general reactions were observed during treatment, neither being alarming. The authors feel that the chief value of this therapy lies in its capacity for initiating remissions of symptoms. Cure should not be anticipated. It is their opinion that foreign protein therapy should not replace the usual management of peptic ulcer, but may be exhibited as an auxiliary treatment in selected instances. It can be employed with fair expectations of insuring temporary relief at no risk to the patient.

Hufford (39) has treated a large series of patients with subcutaneous injections of vaccine made from streptococci obtained from ulcers of human beings. Injections were given twice weekly; the dosage was started at 0.1 c.c. and was increased from 0.1 to 0.2 c.c. each injection until 1.0 c.c. was reached, and this was continued for 8 to 10 consecutive weeks. Of the entire group of 154 patients with ulcer in his private practice in the period of four years, 116 were treated with the stock ulcer vaccine in addition to diet and oral medica-

tion. Seventy-one of this group had all evident foci of infection removed, and ulcer of two only has recurred, an incidence of 2.8 per cent. Forty-five of the 116 patients received inoculations of ulcer vaccine but did not have all foci eradicated, and the ulcers of eight (17.8 per cent of 45) recurred in from one to three years. Thirty-four patients of the 154 did not receive inoculations of ulcer vaccine in addition to the usual regimen for ulcer but 18 of the 34 had all evident foci of infection removed, and the ulcers of eight (44.4 per cent of the 18) have recurred to date. Among the 16 patients of the 34 who did not have foci completely eradicated, ulcers of thirteen (81 per cent of 16)recurred. Four patients of the 154 received surgical treatment only.

The clinical results in this series of cases of ulcer seem to demonstrate that ulcer vaccine and removal of foci of infection are two indispensable adjuncts to the usual dietetic and hygienic measures, and offer more successful means of combating this chronic and recurring malady.

This series of cases is not large enough and the element of time is too short to draw any definite conclusions, but two deductions can be made: (a) that foci of infection seem to play an important part in the production of ulcer, and (b) that immunity, at least for a time, can be obtained

by the use of vaccine made from streptococci obtained from ulcers of human beings, and having definite localizing properties when inoculated in animals. This would seem to substantiate the opinions long held by Rosenow.

Martin (53) studied the effect of the injection of non-specific protein, in most cases milk, injected intramuscularly in 10 c.c. doses on alternate days for six or more injections. If the patient is particularly sensitive to milk, one of many other non-specific proteins may be used. Evidence has been advanced that duodenal ulcer in man may be the result of a reaction of sensitized cells to a specific antigen, and it is thought by this author that the therapeutic aid brought about by parenteral injections of milk protein may be due to a non-specific desensitization of the sensitized cells. He feels that the beneficial results are not due to reaction or shock which is produced only occasionally by accident.

Such treatment was given to 95 ulcer patients by this author. Of these 78 per cent were greatly improved or clinically cured at the end of treatment. At this time a greater percentage of those patients, whose symptoms had existed for only a few months, were clinically cured or improved, that is 85 per cent. One to four years after treatment, 60 per cent of the 60 cases who reported were

clinically cured or improved. Of those whose symptoms had existed less than one year prior to treatment, 80 per cent were improved or clinically cured. The majority of these patients had been on a general diet.

Meyer and Kartoon (54) studied the effect of intravenous injection of killed typhoid bacilli and gonococci on eleven cases of peptic ulcer. Their conclusion from this series was that non-specific protein should be considered only as an adjunct in the treatment for peptic ulcer. They find that the relief from pain during this treatment is independent of changes in acidity. It is their belief that the diminution in gastric tonus and contraction which occurs following injections of foreign protein as well as the increased vascularity in the capillary bed in and about the ulcer are factors in the relief from pain. These men advanced the hypothesis that rhythmic pain in ulcer is due to rhythmic variations and disturbances in the vascular bed in and about the ulcer, associated with digestive peristaltic activity.

Intravenous Sodium Chloride and Sodium Citrate Therapy

It has been stated earlier that one of the theories for the production of peptic ulcer is based on the presence of a circulatory disturbance in vulnerable areas of the upper portion of the gastro-intestinal tract. Working along this

line of thought a method of therapy for peptic ulcers has been developed which consists of the intravenous injections of a solution containing sodium citrate and sodium chloride buffered to the correct hydrogen ion concentration with a buffer salt. Following are the factors, according to Butman, Schultz, and Van Kleek, (15) that have led to the use of this combined solution in the treatment of peptic ulcer.

As is well known, sodium chloride has been used in several forms for medical and surgical purposes and has proved to be of great value. In the preservation of cellular and tissue life it has served with much success. Its role in aiding the circulatory processes, improving blood condition, preventing shock, nausea, vomiting, etc., is also well recognized. Sodium chloride in the form of saline has been used for local dressings by many authorities. It has been injected into the body for its effect in fighting infection and for circulatory aid. It has been used successfully for the reduction of blood viscosity. It has been used with markedly beneficial results in the treatment of thromboangitis obliterans.

The anticoagulating properties of sodium citrate have been recognized for years. Its use in blood transfusions and for the preservation of the blood as a fluid for analytical purposes is generally accepted. It has been used,

with notable success, in the treatment of thromboangitis obliterans and pneumonia. It apparently is the contention of students of the circulatory processes; that sodium citrate lessens the tendency toward clotting, aids the direct formation of a collateral circulation where there is a demand. It has been shown by Normet, through his studies upon animals and humans, that citrate has the property of stimulating a healing of the tissues. Even after removal of large quantities of blood, a survival of the individual organs or even the animal itself was apparent, following the injection of citrate. Sodium citrate has been described by Schultz as a stimulant ih the formation and preservation of red and white blood cells. Its property of reducing shock and its benefit in the treatment of pernicious anemia are well recognized. It is apparent that sodium citrate has many attributes and deserves considerable recognition for its healing, preservative and stimulating qualities, together with its important role in the treatment of the circulatory disturbances as a fluidifying agent.

The healing of peptic ulcers by this treatment, according to Kohn (44), is attributed: (a) to an improvement in the direct and collateral circulation in the region of the ulcer, (b) to a lessening of the tendency toward thrombosis within these vessels, (c) to improvement in the chemical

balance of the blood, (d) to increased resistance of the tissues against autodigestion, and (e) to increased resistance of the blood against infection and other disease processes occasioned by the tonic influence exercised upon the hemopoietic organs, the reticuloendothelial system, and other important parts of the body.

Kohn further states that this treatment aids in clearing up spasms caused by local gastric or duodenal irritability and seems to otherwise regulate muscle tonus and perestalsis. The employment of alkalies and the adherence for a long period of time to a bland non-irritating diet, will enable the intravenous treatment to bring about a quicker and more effective response in most cases. This author reports markedly beneficial effects following this treatment in a series of intractable cases. Symptomatic cure or improvement occurred in about 80 per cent of the number. The other cases also showed improvement, but not of a decided nature.

Butman, Schultz, and Van Kleek (15), and others associated, report over one hundred cases treated by this method with good immediate results. In all cases the symptoms disappeared. The treatment consisted of 10 c.c. given intravenously for the first dose and thereafter 20 c.c. two or three times a week except in very severe cases, it was given every 24 hours. Twenty-four doses were given which were

usually followed by one every three or four weeks for a year to minimize recurrence. The authors have experienced no untoward symptoms or reactions in their series, thus indicating its apparent safety. Ulcer complicated by hemorrhage was found to be no contraindication to this form of therapy. The use of the solution permits from the onset a more liberal diet for the patient, except in those cases complicated by hemorrhage. The allowance of a working diet from the onset is important and greatly appreciated by most ulcer patients.

Because of the short period of observation of the patients treated by this method when these reports were made, no positive statement as to permanent cure can be made.

For years Holler, Pribram, Mueller and Petersen (62) and others have been working with various proteins to control gastric functions and check the hypermotility of the stomach. They were able to stimulate the vegetative nerves and produce hypoperistalsis, lessen the amount of free hydrochloric acid, induce a hyperemia and increased vascularity about the ulcerated area in the gastric mucosa, as well as augment the production of gastric enzymes and total lipoids. However, they were able to control these physiological functions only for one and one-half to two hours, which is of little therapeutic value in peptic ulcer.

By reinforcing the protein with lipoids and lipins, a more sustained action was obtained. Finally it was found

that emetine acted as a synergist in such a manner that it was possible to control the gastric functions for a period from 96 to 120 hours with one intravenous injection. The combined solution has also a decided cumulative action so that after the fifth or sixth injection, hypoperistalsis, increased vascularity, muscular relaxation, and dilation of the stomach are maintained for a period of more than 240 hours. There is also an increased flow of gastric juice containing a relatively low hydrochloric acid percentage and adequate enzymes. These induced phenomena make the patient comfortable, free from pain, and promote healing of the ulcer. The solution also increases the resistance of the tissues about the ulcer and produces an anti-bacterial action on the causative microorganisms.

Pitkin (62) treated 127 patients with peptic ulcer by this combination of substances in which the protein used was derived from schizomycetes. The injections were usually given at three-day intervals, the total number usually being eight or more, depending on the results. Seventy-six patients were relieved by the first injection and all but nine of the remaining were relieved later. The permanency of the results had not been determined at the time this report was made.

Emetine Hydrochloride

Olpp (60) believes that emetine may be regarded as specific in simple gastric and duodenal ulcer, as in upwards of 400 cases its administration has always been followed by a prompt alleviation of the painful symptoms and, in most cases, ultimate complete recovery.

The drug is given intravenously by him every other day until six injections have been administered and then a week of rest after which, if necessary, three more injections are given. He has found that not more than nine are needed. While the injections were being given the patients were put on a soft diet and alcohol prohibited.

Olpp has given 10,000 intravenous injections of emetine and has never had a serious reaction.

Cunha (19) reported on a mixture of emetine and lipoprotein known as "Synodal". He treated 51 patients with peptic ulcer by injecting one ampoule of synodal every fourthday for ten injections. During this time the patients were on a soft diet. When the report was made the treatment of 29 cases had been completed over a year and 22 during the past twelve months. In all but two cases relief from pain occurred promptly. According to Cunha, synodal produces those structural changes, as evidenced by radiographic studies, which are associated with healing of the ulcer.

At present most authorities are agreed on placing little value on emetine in the treatment of peptic ulcer.

Insulin Therapy

The first suggestion concerning the value of insulin in the treatment of ulcerative lesions came from the empirical observations on ulcers of the toes or feet in diabetics following the routine injection of insulin given for the diabetes. It was subsequently shown that insulin applied as a wet dressing locally over the ulcer of a diabetic's foot or toe, likewise induced wound healing. Later, non-diabetic varicose ulcers of the leg were found to react similarly. These bedside experiences furnished a rational basis for the trial of insulin in cases of peptic ulcer.

It was soon realized, however, that insulin given by mouth would promptly leave the stomach and hardly remain in contact with the ulcerated area long enough to exert an effect. The problem, therefore, of retarding the evacuation of insulin from the stomach next presented itself. Several methods of combining insulin with inert substances which would inhibit the gastric motility and leave the insulin unchanged were tried. The material that was finally selected for this purpose was bismuth subcarbonate because it logically entered into the therapeutic routine of gastroduodenal

ulcer. This substance forms a loose physical combination with insulin, reduces gastric hyperperistalsis by mechanically coating the ulcer, and releases the insulin slowly, so that the latter may act on the ulcerated area of the gastric mucous membrane. In three to seven days, there was usually complete symptomatic relief in patients treated by this method, according to Danzer (20).

In Jones' opinion (41), a vagotonic constitution being a part if not wholly the predisposing cause of ulcer, offers an hypothesis upon which to base the rationale for the use of insulin as a treatment for ulcer per se and not merely to improve nutrition. It has been noted that improved nutrition was accompanied by a modification of the vagotonic syndrome, that is, a change from vagotonus to normotonus, thus reducing the acid secretion of the stomach and modifying the spastic condition of the organ. Aschoff, who puts great stress on the "spastic influences", states that due to the cramp-like, severe contraction of the musculature, a kinking of the vessels occurs and thus a localized hyperemia with resulting hemorrhage or local stasis. Blood engorgement and spastic contraction act together in producing a venous-stasis hyperemia and a venous hemorrhage on the summit of the fold system, of the lesser curvature, the gastric pathway. This spasticity is relieved by a return to normotonus.

Jones (41) treated 25 patients with peptic ulcer by injecting into them 10 to 20 units of insulin subcutaneously three times a day, and maintaining them on a high carbohydrate diet. He divides the patients into three groups depending on the type of ulcer they had.

Group I. Twelve patients with fresh peptic ulcer.

In 7 pain gone in 5 days, blood in stools gone in 7 days.

In 4 symptoms gone in 6 to 10 days.

In 1 symptoms gone in 2 weeks.

After 10 to 15 days x-ray showed no sign of ulcer. In six patients there were no complaints for 5 to 7 months. In two patients without special diet after $3\frac{1}{2}$ to $4\frac{1}{2}$ months there was a disposition toward increased vagotonus and some pain after eating but blood in the stool and x-ray findings were negative.

Group II. Five patients with recurrent ulcer were given 20 to 30 units of insulin a day for 2 to 3 weeks. Symptoms of all disappeared in from 7 to 10 days. Four of these patients were watched from 9 to 15 months without recurrence of symptoms. In one there was a recurrence of symptoms in $5\frac{1}{2}$ months but they were again relieved by further injections.

Group III. Eight patients with complicated ulcer were partially but not completely relieved of symptoms in 14 to 16

days of treatment.

This report indicates that insulin has been beneficial in relieving symptoms in a certain number of uncomplidated ulcers, and is especially helpful in patients showing a high degree of vagotonia.

PHYSICOTHERAPY

According to Snell and Bollman (75), irradiation with roentgen rays of the intact upper portion of the abdomen of dogs produces a variable and temporary reduction in the gastric acidity and a definite destructive effect on gastric mucosa. It is not possible to maintain a consistently low level of acidity for any prolonged period without the production of actinodermatitis or "radiation sickness". Irradiation of the surgically exposed and isolated stomach produces a similar effect on gastric secretion which effect is also temporary. Larger single doses are required to produce such an effect. Subsequent irradiation of the intact upper portion of the abdomen of these animals reduces gastric acidity but permanent anacidity has not been attained by this means.

It is suggested that the reported symptomatic improvement of patients affected with ulcer who have received irradiation by roentgen rays may be due to an effect on local leukocytic infiltration rather than to a direct effect on

gastric secretion.

According to Levy (46), the physiological effects noted in the use of ultraviolet radiation are: (a) improved circulation, (b) increased appetite and weight, (c) increased height in children, (d) disappearance of insomnia when present,(e) normalization of endocrine gland function, and (f) general tonic effect by balancing the sympathetic=parasympathetic divisions of the autonomic nervous system.

Effects noted in the use of infrared radiation are: (a) vasodilation in superficial and deep tissues and betterment of lymph circulation, (b) the stomach is brought to rest by the heat produced, and (c) the radiation has an analgesic effect.

For these reasons Levy had treated over 200 cases of acute and chronic peptic ulcer by ultraviolet and infra-red radiation by 1932. Ninety per cent of the cases treated were cured as evidenced by disappearance of symptoms and the radiographic niche. In these cases there were no recurrences in from two to ten years according to the author.

In addition to the rays the patients received a bland ulcer diet, alkalies three to six times daily after meals as needed, and a general sedative if needed. They received a minimum of thirty treatments at the rate of three a week.

FOOD IDIOSYNCRASY

Simon (73) states that in treating peptic ulcer, the possibility of food idiosyncrasy should be kept in mind. Milk, eggs, and wheat make up a large part of the diet of many ulcer treatments and these foods are the most commonly reacted to. An idiosyncrasy may be independent of the ulcer or it may be related in which case withdrawl of the offending food relieves symptoms. In many cases an idiosyncrasy may produce the symptoms of ulcer when there is no lesion present. This factor then, should always be kept in mind when treating ulcer patients.

OTHER TREATMENTS FOR PEPTIC ULCER

There have been reported isolated articles on other types of proposed peptic ulcer therapy in the English, American, and Australian literature in the past few years. In all of these, as well as in many of those already discussed, many more observations must be made on the treatments before any true appraisal of their value may be made. Among these are the following; bromide and belladonna therapy (69), oral administration of metaphen (77), pepsin therapy (34), administration of parathyroid (27), treatment with digitalis (38), duodenal extract therapy (65), and the use of hydrated magnesium trisilicate (56). All of these various methods have their champions and due consideration must be

given those which prove their merit in a rather lengthy series of cases.

CONCLUSIONS ON METHODS OF TREATMENT

It has been shown in this paper that various students of the problem of peptic ulcer have very different ideas as to what constitutes a satisfactory therapeutic approach to the subject. The writer of this discussion has no right to voice an opinion based on clinical experience, so it becomes necessary to observe the consensus of opinion. It appears at the present time that cases of recent uncomplicated ulcer can be well managed in most instances on an ambulatory regimen of diet, similar to that suggested by Alvarez. Occasional alkalies may be useful in controlling symptoms but their use in attempting to completely control the acid factor appears in many cases very difficult and of doubtful importance unless nearly complete and constant anacidity are attained. The use of alkalinized powdered milk tablets should prove a very useful and convenient form of feeding and gastric control between the regular meals.

It would seem that a complete Sippy regimen might be indicated in more chronic cases and those in which more imperfectly controlled treatments have been tried without much success. It also would seem advisable to subject a patient to this mode of therapy before surgery is attempted in an

effort to give the ulcer the opportunity of healing under very favorable conditions.

In cases where the diet and alkalies fail to produce a remission, mucin may be tried, for it is quite well proven that this substance is effective in a large number of cases not affected by the diet and alkalies.

Other methods of treatment which appear to be sound are those of the continuous alkalinized milk drip and continuous aluminum hydroxide drip procedures. These necessitate bed rest and give the opportunity of completely neutralizing the gastric contents over the desired length of time which is no doubt of great value in stubborn cases. When these methods of treatment have been used over a longer period of time they will probably gain wide recognition for the treatment of difficult cases.

If none of these methods appear to be helpful surgery must be considered, the procedure depending entirely upon the case, the judgment and skill of the operator. It appears to be a general rule, however, to avoid doing a gastro-jejunostomy on young patients with high gastric acidity and rapidly emptying stomach for these patients, in many cases, develop a new and more resistant marginal or jejunal ulcer.

In cases where surgery is opposed, histidine may be tried which may give a satisfactory result in cases refractory

to other methods of treatment.

Atropine, belladonna, and related substances are drugs of merit in many cases as adjuncts to the fundamental type of therapy.

As for other types of treatment mentioned and discussed, it is left up to the individual physician to try their results if they care to do so. There are probably cases which have been treated thoroughly by the more tried and accepted means of therapy and failed, which may be helped by less-well recognized treatments. Additional case observations on these newer treatments will either prove their merit or cause them to be discarded to make room for new methods to come. So it is that medicine progresses.

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